The New England
Journal of Medicine

Copyright, 1946, by the Massachusetts Medical Society

Volume 234 FEBRUARY 28, 1946 Number 9

MEDICAL SHOCK: ABNORMAL BIOCHEMICAL CHANGES IN PATIENTS WITH SEVERE, ACUTE MEDICAL ILLNESSES, WITH AND WITHOUT PERIPHERAL VASCULAR FAILURE*

CHARLES S. DAVIDSON, M.D.,† JESSICA H. LEWIS, M.D.,‡ HENRY J. TAGNON, M.D.,§
MARGARET A. ADAMS, A.B.,¶ AND F. H. L. TAYLOR, PH.D.||

BOSTON

RECENT studies in the so-called "shock syndrome" in animals have definitely associated this syndrome with certain biochemical abnormalities.[1,2] Hyperglycemia, lactacidemia, lowered alkaline reserve and changes in the partition of the nonprotein nitrogen of the blood plasma have been reported in this condition. In hemorrhagic shock, increases in the plasma alpha amino nitrogen have recently been reported.[3,4] Anoxia has been a frequent finding in shocked animals, and furthermore, anoxic anoxia itself has been found to produce some of the biochemical changes attributed to shock.

Recent reports from this laboratory have shown that in man marked biochemical changes of a similar nature to those reported in animals occur following thermal burns.[5,6] Such changes were found to be significantly associated with the severity of the thermal injury and the presence of shock. Aub[7] has reported abnormalities of carbohydrate metabolism following trauma.

The present investigation was undertaken to study the relation of peripheral vascular failure, uncomplicated by traumatic conditions, to the biochemical changes previously reported in shocked animals and following injury in man. The subjects used were patients suffering from severe medical illnesses, with or without the presence of peripheral vascular failure. In all cases there was no indication in the history that clinical diabetes was present.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital, and the Department of Medicine, Harvard Medical School.

The work described in this paper was done in part under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

†Instructor in medicine, Harvard Medical School; assistant physician, Thorndike Memorial Laboratory; assistant director, Second and Fourth Medical Services (Harvard) and junior visiting physician, Boston City Hospital.

‡Research fellow, Harvard Medical School; research fellow, Thorndike Memorial Laboratory, and assistant in medicine, Boston City Hospital.

§Francis Weld Peabody Fellow and instructor in medicine, Harvard Medical School; research fellow, Thorndike Memorial Laboratory, and assistant in medicine, Boston City Hospital; tutor in biochemical sciences, Harvard University.

¶Laboratory assistant, Thorndike Memorial Laboratory, Boston City Hospital.

‖Associate in research medicine, Harvard Medical School; chemist, Thorndike Memorial Laboratory, Boston City Hospital.

METHODS

Twelve patients suffering from severe illnesses were studied. Their ages ranged from nineteen to eighty, 9 patients being over fifty years of age. There were 7 males and 5 females. No patient gave a history or had clinical evidence of diabetes mellitus. Five patients were admitted with severe infections; 4 with severe cardiovascular involvement, 1 of whom suffered from pneumococcus (Type 1) pericarditis; 2 following the ingestion of poison, probably an overdose of a barbiturate; and 1 with a massive gastric hemorrhage. Ten patients had some degree of peripheral vascular failure, the degree being estimated independently by two physicians. The criteria used in estimating the degree of failure are shown in Table 1. The essential details of the cases studied are given in Table 2. The patients were treated by specific or symptomatic therapy in accordance with the requirements of their clinical condition. Where such therapy had a bearing on the biochemical changes encountered it is commented on in the appropriate place in the text. Autopsies were obtained on certain patients who died, and the significant findings are stated in the text.

Blood and urine samples were obtained during and following the period of circulatory failure and analyzed for glucose (Somogyi–Benedict method), lactic acid, carbon dioxide content or combining power, alpha amino nitrogen (ninhydrin method) and oxygen. Tolerance for glucose was frequently determined by the intravenous method.[8] Prothrombin times, icterus indices and hemoglobin levels were determined. The methods used for the various determinations have been stated elsewhere.[6]

RESULTS

The over-all data are presented in Table 3. They are arranged in order of decreasing lactic acid concentration in the blood plasma or serum. To arrive at the designation of the degree of peripheral

vascular failure, the clinical criteria given in Table 1 were used without reference to the biochemical findings. The data chosen for the construction of the table were those obtained at a time when the peripheral vascular failure was present to the greatest extent. Variations in the blood chemical findings in certain typical patients are presented in the figures.

The Relation of Biochemical Abnormalities to the Presence of Peripheral Vascular Failure

Abnormalities in carbohydrate metabolism. Hyperglycemia was found in 9 of the 10 patients showing some degree of peripheral vascular failure. The tenth patient was poorly nourished. There was

Lactacidemia was found in all patients showing any degree of peripheral vascular failure, regardless of the clinical diagnosis. The correlation between the concentration of lactic acid in the circulating blood and the degree of peripheral vascular failure was striking. As might be predicted, in general the carbon dioxide content or the combining power varied inversely with the lactacidemia, although there was no evidence that the change in the alkaline reserve varied quantitatively with the amount of lactic acid. Other fixed organic acids were not determined. The lactic acid levels ranged from 4 to 20 milliequiv. per liter of plasma or serum. In 2 cases (Cases 8 and 10) in which no peripheral

TABLE 1. *Criteria Used in Estimating the Degree of Peripheral Vascular Failure.**

Degree of Peripheral Vascular Failure	Respiration†	Pulse*	Blood Pressure	Mental State	Cyanosis	Extremities	Oliguria
Minimal (+)	Normal	Thready and rapid	Slight fall	Restless and apprehensive	Lips or extremities or both	Pale and cool	None
Moderate (++)	Rapid and shallow	Thready and rapid	80/60 to 60/40	Apprehensive and confused	Lips or extremities or both	Cold and clammy	Questionable
Marked (+++)	Often Cheyne-Stokes or sighing	Thready and rapid	60/40 to 40/20	Confused to stuporous	Lips or extremities or both	Cold and clammy	Slight
Extremely marked (++++)	Often Cheyne-Stokes or sighing	Rapid, slow or unobtainable	40/0 to 20/0	Stuporous to comatose	Extremities mottled (extensive)	Cold and clammy	Moderate (often albumin, red cells and casts)

*Temperature, nausea and vomiting were not used as general criteria because of the fluctuations due to causes other than peripheral vascular failure. The effect of the *duration* of the failure was taken into consideration in evaluating the biochemical findings (see Table 3).

†Unless modified by the clinical condition — for example, pneumonia.

minimal or no elevation of the blood glucose in the 2 patients in whom peripheral vascular failure was absent. One of these patients (Case 8) suffered from streptococcal pneumonia and recovered. The other (Case 10) was poisoned, presumably by barbiturates, and subsequently died.

There was no correlation between the height of the blood glucose and the degree of peripheral vascular failure. In 3 cases (Cases 3, 4 and 11) this type of comparison was impossible because of the necessity of administration of glucose for therapeutic reasons.

Glucose-tolerance determinations were made in 8 patients. In the patients who survived long enough, the blood-sugar levels had returned to normal prior to discharge. Glycosuria of slight degree was found in 2 patients. In none of the patients with abnormalities in the tolerance for glucose was the presence of diabetes mellitus discovered by the history, and in none of those who recovered was it shown by subsequent observations of the glucose level. In 3 patients, the ability to handle the added glucose was unimpaired, although the blood-sugar level was elevated. In the other 5 patients, the blood glucose was elevated at the end of two hours following a test dose of 25 gm. intravenously.

vascular failure was present, the values were approximately normal, being 2 milliequiv. per liter in each case.

Abnormalities in the alpha amino nitrogen concentration of the plasma or serum. The standard deviation from the mean of random determinations of the alpha amino nitrogen shown in the literature and in our own data is ± 0.4 mg. The mean for normal values is 4.1 mg. per 100 cc. of plasma.[9,10]

Although it is known that increases in alpha amino nitrogen occasionally occur in serum left in contact with cells,[11] determinations of this substance were made occasionally on serum as a matter of convenience. When this was done, the cells were removed as rapidly as possible and hemolysis was absent. For statistical purposes, no alpha amino nitrogen value was accepted as elevated that did not deviate from the mean by more than four times the standard deviation. In other words, it was accepted that the probability was only 1 in 1000 that an alpha amino nitrogen value above 6.0 mg. per 100 cc. of plasma or serum was due to chance alone. On this basis, 4 of the 10 patients with peripheral vascular failure had elevated alpha amino nitrogen values. These patients (Cases 3, 5, 7 and 12) had marked (+++) or extremely marked (++++) peripheral vascular failure.

At the same time it should be noted that the patients in Cases 3, 5 and 12 showed evidence of liver damage, as indicated by an increased prothrombin time and an elevated icterus index. Furthermore, the patient in Case 12 showed unmistakable evidence of cirrhosis of the liver at autopsy, and the patient in Cases 5 and 7 gave evidence of acute liver damage on histologic examination. The patient in Case 3 showed clinical evidence of previous liver damage. The great majority of patients with more than moderate (++) peripheral vascular failure, however, showed an increase in either the icterus index or the prothrombin time, or both, without any significant increase in the plasma alpha amino nitrogen.

Blood oxygen and arteriovenous oxygen differences (femoral). There is no evidence from the data in Table 3 that there is any degree of correlation between the oxygen content or saturation of the arterial or venous blood and the degree of peripheral vascular failure. Five patients with marked (+++) or extremely marked (++++) peripheral vascular failure, however, showed an arterial oxygen saturation of 85 per cent or less, 100 per cent hemoglobin being considered equivalent to 20.9 vol. of oxygen per 100 cc. of blood. The patient in Case 3 had a marked anemia from blood loss, as well as a marked unsaturation of the remaining hemoglobin. In all other cases, the patients had either a normal or a somewhat elevated hemoglobin concentration. The elevation of the hemoglobin did not show a great deal of hemoconcentration in relation to the severity of the peripheral vascular failure. Indeed, the patient in Case 10, who had no peripheral vascular failure, had the highest hemoglobin concentration — 117 per cent. The patients in Cases 9 and 10 had low arteriovenous oxygen differences. In Case 9, cyanosis and peripheral vascular failure were present but both the arterial and venous saturations were normal, which suggested that the circulating blood was a poor index of the anoxic state of the obviously cyanotic and probably anoxic tissue.

Studies of the Biochemical Abnormalities in Certain Cases

Typical cases from the group of patients with infection or various cardiovascular conditions and a case of probable barbiturate poisoning will be presented. Each of these patients had at least marked (+++) peripheral vascular failure in association with the severe illness.

TABLE 2. *Clinical Data on Patients with Severe Medical Illnesses.*

Case No.	Type of Illness	Age	Sex	Degree of Peripheral Vascular Failure	Final Outcome
		yr.			
	Infection:				
	Pneumonia:				
2	Pneumococcal (Type 7)	57	M	+	Recovered
9	Pneumococcal (Types 3 and 14)	62	F	+	Recovered
8	Streptococcal	19	M	0	Recovered
6	Undetermined	71	M	++	Died (not in peripheral vascular failure)
4	Meningitis (Type 14 pneumococcus)	60	F	++++	Died in peripheral vascular failure
5	Pericarditis (Type 1 pneumococcus)	68	M	++++	Died (not in peripheral vascular failure)
	Cardiovascular disease:				
1	Myocardial infarction with heart block	72	F	+	Recovered
7	Dissecting aneurysm	60	M	++++	Died in peripheral vascular failure
12	Mesenteric thrombosis	80	M	+++	Died in peripheral vascular failure
	Poisoning:				
10	Barbiturate (?)	32	M	0	Died (not in peripheral vascular failure)
11	Barbiturate (?)	30	F	++++	Died in peripheral vascular failure
3	Gastrointestinal hemorrhage	54	F	+++	Died in peripheral vascular failure

CASE 5. *A 68-year-old man with pericarditis (pneumococcus, Type 1); peripheral vascular failure estimated at ++++.*

This patient had been suffering from a vague illness associated with epigastric pain and constipation of 10 days' duration. He was seen by his physician on the day previous to admission, at which time the pulse, temperature, heart and lungs were reported to be normal. Shortly before admission he became extremely dyspneic and mentally confused.

Examination on admission revealed a well developed and well nourished elderly man suffering from marked respiratory distress. The blood pressure was unobtainable. The femoral pulse was 180, the respirations 40, and the rectal temperature 97°F. The patient was mentally confused, irrational and apprehensive. The skin was cold and dry, with mottled cyanosis of the extremities as well as of the lips and nail beds. Examination of the lungs revealed medium moist rales throughout both lung fields. On percussion the heart was 13 cm. to the left and 4 cm. to the right of the midsternal line. The sounds were distant and muffled, without murmurs or friction rubs. The radial pulse was not palpable, but the femoral pulse was obtainable and was markedly paradoxical.

A clinical diagnosis of pericardial effusion was made, which was consistent with the electrocardiographic tracings. The patient was accepted for biochemical study and was classified as having ++++ peripheral vascular failure.

During the period of unobtainable blood pressure, marked

biochemical abnormalities were observed (Figs. 1 and 2). The blood glucose was markedly elevated (143 mg. per 100 cc.). The serum lactic acid was 14.6 milliequiv. per liter, and the carbon dioxide content of the serum was reduced to 8 millimols per liter. The serum nonprotein nitrogen was elevated to 276 mg. per 100 cc., and the alpha amino nitrogen was at the extremely high level of 20.0 mg. The arterial oxygen content was 14.0 vol. per cent, which in the presence of a hemoglobin concentration of 84 per cent indicated a saturation of 79 per cent. The Quick prothrombin time of the initial blood was prolonged to 35 seconds (normal, 21 seconds). The icterus index was 12.5.

Shortly after the initial blood was taken, a pericardial tap was performed and 150 cc. of yellowish-green purulent fluid was removed. This fluid and a simultaneous blood culture showed the presence of Type 1 pneumococcus. Twenty-five thousand units of penicillin in 25 cc. of saline solution was instilled in the pericardium by a second tap. A pericardial exploration was made, at which time a further 200 cc. of purulent fluid was removed from the pericardium. A catheter was inserted into the pericardium and used for irrigation with penicillin.

Immediately after the first pericardial tap, the blood pressure rose to 70/50 and there was marked relief of respiratory distress. The second blood sample was obtained 7 hours after the first and 5 hours after the pericardial tap. At that time there was no evidence of peripheral vascular failure, nor did it later recur. The blood glucose on this sample had risen to 172 mg. per 100 cc. In subsequent samples it fluctuated between 155 and 225 mg. until the 3rd hospital day.

A glucose-tolerance test was made from the 4th to the 6th hour after the initial blood was taken. It was grossly abnormal. Unfortunately, the blood glucose was at a high level at that time and continued to rise during the subsequent 5 hours. The interpretation of the finding is therefore extremely difficult.

A sample of heart blood taken just prior to death on the 4th day gave a low level of glucose (39 mg. per 100 cc). The

TABLE 3. *Biochemical Data at Time of Greatest Peripheral Vascular Failure.*

Case No.	Peripheral Degree	Vascular Failure Onset	Vascular Failure Duration	Glucose	Lactic Acid	Hemoglobin	CO_2 Content	CO_2 Combining Power
			hr.	*mg./100 cc.*	*mE./l.*	%	*mM./l.*	*mM./l.*
4	++++	Slow	12	234*	20	93	12	—
7	++++	Acute	2	332	16	83	—	17
5	++++	Slow	?	143	15	84	8	—
3	++++	Acute	12	552*	14	36	11	—
11	++++	Slow	36	370*	12	101	15	—
12	+++	Slow	?	122	8	101	36	—
6	++	Slow	?	79	6	102	—	24
1	+	Acute	16	178	6	88	—	21
2	+	Slow	54	122	5	81	—	26
9	+	Slow	?	146	4	105	25	—
10	0	—	—	97	2	117	24	—
8	0	—	—	86	2	84	—	19

*Glucose administered parenterally.

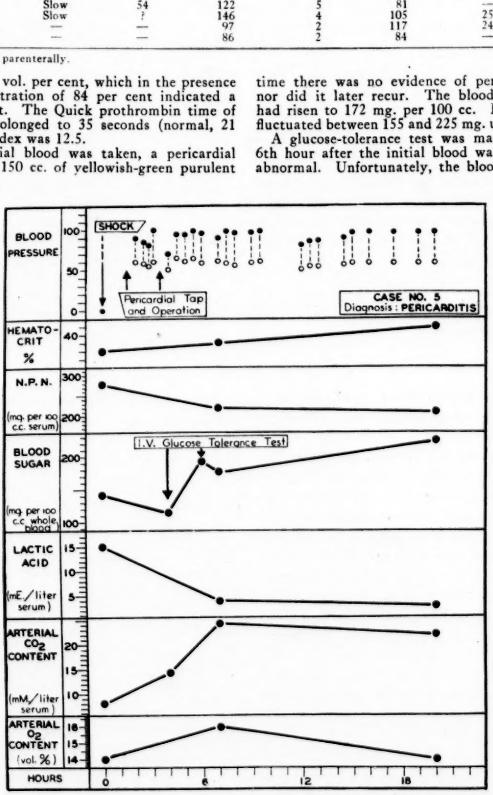

FIGURE 1.

serum lactic acid level fell promptly after return of the blood pressure to relatively normal levels, falling from the initial level of 14.6 to 4.0 milliquiv. per liter. Subsequent levels taken at varying intervals of time until death gave values of 3.2 and 3.6 milliequiv.

The carbon dioxide content rose rapidly from the initial level of 8 millimols per liter to 24.5 millimols as peripheral vascular failure subsided, and remained at these normal levels for the 24 hours over which observations were made. There was no important statistical change in the oxygen content, although the oxygen saturation rose to 91 per cent after the operation but in 24 hours had fallen to 75 per cent of saturation.

The nonprotein nitrogen remained above 200 mg. per 100 cc. until death, but the serum alpha amino nitrogen fell promptly after operation from 20 to 10 mg., at which high level it continued until the patient's demise.

The icterus index and the prothrombin time both remained elevated until death. Oliguria was present from admission and gradually became progressive. The clinical picture of uremia was present and was progressive. In spite of the improvement in the respiratory distress and peripheral failure, the patient remained mentally confused, with a uremic odor on the breath and a uremic frost on the face, until death.

Autopsy. The kidneys were grossly normal. They stripped easily and were of average size and weight. Histologically there were no essential abnormalities except acute edema and congestion. The liver microscopically revealed marked central necrosis, but it was thought that the morphologic findings were consistent with an acute rather than a chronic change.

TABLE 3 (*Concluded*).

Case No.	Oxygen Saturation		Arteriovenous Oxygen Difference	Icterus Index	Alpha Amino Nitrogen	Quick Prothrombin Time†	Outcome	Liver Disease at Autopsy
	Arterial	Venous						
	%	%	*vol. %*		*mg./100 cc.*	*sec.*		
4	83	11	14	10	4.7 (plasma)	38	Died	No autopsy
7	—	—	—	6	6.5 (plasma)	—	Died	+ (acute)
5	79	—	—	13	20.0 (serum)	35	Died	+ (acute)
3	65	—	—	75	7.3 (serum)	53	Died	No autopsy
11	81	—	—	9	5.2 (serum)	46	Died	+ (acute)
12	59	32	6	11	6.1 (serum)	30	Died	+ (chronic)
6	—	—	—	6	4.1 (plasma)	31	Died	+ (acute)
1	—	—	—	4	3.9 (plasma)	19	Living	
2	—	—	—	13	2.9 (plasma)	25	Living	
9	91	79	4	4	4.0 (serum)	25	Living	
10	74	71	1	4	—	—	Died	+ ?
8	—	—	—	6	4.1 (plasma)	26	Living	

†Normal, 21 to 26 seconds.

CASE 7. *A 60-year-old man with dissecting aneurysm of the aorta; peripheral vascular failure estimated at* ++++.

Three hours before admission the patient developed a dull, aching pain at the anterior base of the neck, without radiation. Shortly afterward he experienced a dull, aching, "smother-

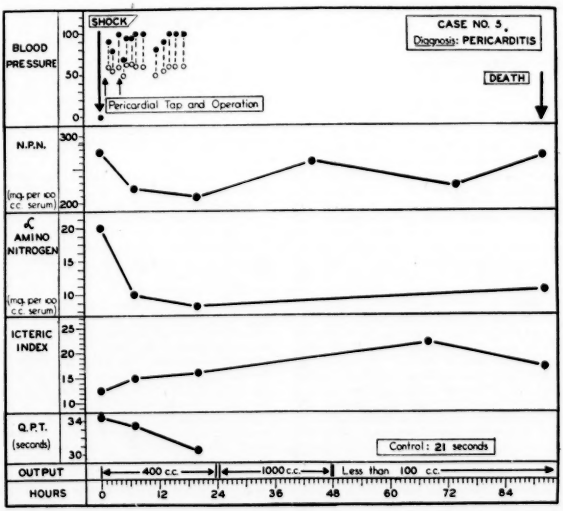

FIGURE 2.

ing" pain over the precordium. This was followed by collapse and loss of memory until after arrival at the hospital. On recovery of consciousness, the patient complained of abdominal cramps and a desire for defecation. At no time was there radiation of pain. The past history revealed excellent health, without evidence of diabetes or kidney, liver or heart disease and was irrelevant, with the exception of a

single attack of "angina" 15 years previously. A brother was known to have died of a "ruptured aorta."

Physical examination revealed a well developed, well nourished man complaining of moderate precordial and abdominal pain. The pulse was 110, the rectal temperature 97°F., the respirations 25, and the blood pressure 40/20. The extremities were cold, clammy and cyanotic, and a mottled blue discoloration was observed over the flanks. The lungs were clear, but breathing was slightly labored. There was slight venous distention in the neck. The heart was not enlarged, but the sounds were distant and indistinct. The radial pulse was not palpable. The abdomen was soft, but some periumbilical tenderness could be elicited on deep palpation. The electrocardiographic record showed sino-auricular tachycardia and a slightly abnormal ST segment, which was interpreted either as being due to the heart rate or as being consistent with the presence of myocardial disease. A diagnosis of dissecting aneurysm of the aorta was made.

Although the patient received 1500 cc. of saline solution, 500 cc. of plasma and coramine, caffeine, morphine and oxygen, he remained cyanotic, with no obtainable blood pressure after the 1st hour. Seven and a half hours after admission he became irrational, and 2 hours later he died.

Only one set of blood samples was obtained for analysis. These were collected immediately after admission, when the blood pressure was 40/20. Blood was obtained for glucose determinations alone on two occasions when the blood pressure was unobtainable. The blood sugar on the initial sample was 332 mg. per 100 cc. and increased during the next 3 hours to 446 mg. The blood lactic acid was at the high level of 15.7 milliequiv. per liter of plasma. The carbon dioxide combining power was 17 millimols per liter. A glucose-tolerance test showed the initial blood glucose to be 446 mg.; 2 hours after the injection of 25 gm. of glucose it was 351 mg. During this period the patient also received 500 cc. of therapeutic plasma containing not less than 20 gm. of glucose. The nonprotein nitrogen was normal, but the plasma alpha amino nitrogen on the initial sample was elevated to 6.5 mg. per 100 cc.

Prothrombin times were not obtained, and the icterus index was normal.

Autopsy. The liver showed acute focal necrosis, and a dissecting aneurysm of the aorta was found.

CASE 11. *A 30-year-old, unmarried woman with presumptive evidence of poisoning by a barbiturate; peripheral vascular failure estimated at ++++.*

The patient had been treated for 2 months prior to entry for a "nervous breakdown," but was in apparent good health the day before admission. During that night the patient was noticed to be breathing heavily. In the morning she was comatose and was brought to the hospital in this condition. The only sedative known to be in her possession was Nembutal.

The past history showed no evidence of diabetes, hypertension or kidney or liver disease. There was no history of trauma, habitual taking of drugs or organic disorder of the central nervous system.

On admission, the temperature was 100°F., the pulse 120, the respirations 26, and the blood pressure 80/60. The patient was comatose and could not be aroused. The breathing was labored, and the skin was cyanotic and cold. The patient's general appearance was described as moribund. Over the back and lower extremities there were numerous first-degree and second-degree burns covering less than 3 per cent of the total body surface, apparently due to the application of hot-water bottles while the patient was in a comatose state. She was treated with oxygen, coramine, caffeine and unknown amounts of picrotoxin. Intravenous fluids were given, together with therapeutic amounts of sulfadiazine. A lumbar puncture was performed. The spinal-fluid pressure was equivalent to 490 mm. of water; the total protein was 30 mg. per 100 cc., and there were 1 white cell and 30 red cells per cubic millimeter.

Thirty-three hours after admission, when the patient was still comatose, additional clinical findings were obtained. The blood pressure was unobtainable. The extremities were cold and cyanotic, although the patient had been receiving oxygen since admission. There were medium and coarse moist rales throughout the lung fields. Examination of the abdomen revealed moderate muscle spasticity and flexion of the legs on deep abdominal pressure. Neurologic examination revealed dilated pupils that reacted slowly to light. Reflexes were absent with the exception of a gag response, which was inconsistently observed.

Lumbar puncture was repeated and showed a normal pressure. The fluid contained only a few red cells. The patient was catheterized, and 80 cc. of urine was obtained during the next 8 hours. The patient died 41 hours after admission. A medicolegal post-mortem examination was performed.

The first blood sample was taken 33 hours after admission, when the blood pressure was unobtainable. The blood glucose was 369 mg. per 100 cc. and in 2½ hours rose to 586 mg. So far as the records show, no glucose was administered after the study was started. Just before death, 8 hours after the initial blood was taken, a sample of heart blood showed a glucose level of 293 mg. per 100 cc.

The serum lactic acid on the initial sample of blood was markedly elevated (11.8 milliequiv. per liter), and the carbon dioxide content of the serum was reduced (15 millimols). The lactic acid level fell slowly, being 8.4 milliequiv. 3 hours later and 7.2 milliequiv shortly before death. A further observation of the carbon dioxide content showed a slight fall (13 millimols per liter) 2 hours after the initial sample.

The nonprotein nitrogen was 66 mg. per 100 cc. on the initial sample and rose to 91 mg. at the time of death. The alpha amino nitrogen remained within normal limits throughout the period of study. The total urine output during the 41 hours following admission was approximately 290 cc., and the specific gravity was 1.030.

The arterial oxygen saturation was 81 per cent on the initial sample of blood and had risen to 87 per cent 3 hours later. The icterus index was normal throughout the course. The prothrombin time was distinctly prolonged, being 46 and 54 seconds (normal, 24 seconds).

Autopsy. The post-mortem findings were superficial burns of the skin, submucosal hemorrhages of stomach and small intestine, bronchopneumonia (right) and acute central necrosis of the liver.

The foregoing cases represent severely ill patients in whom the component of peripheral vascular failure was extreme. The following case represents a severely ill patient in whom peripheral vascular failure was minimal (+).

CASE 1. *A 72-year-old woman with myocardial infarction and complete heart block; peripheral vascular failure estimated at +.*

This patient was admitted 1 year previous to the present entry with a possible acute diverticulitis. At that time there was no evidence from either a clinical or a biochemical viewpoint of any abnormality in the carbohydrate metabolism. Two years before the present admission, there was a gradual onset of dyspnea, palpitation and ankle edema, which never reached severe proportions. Two months before admission, the patient had a 3-hour attack of substernal pain and a choking sensation, which did not recur until 3 days before admission. This attack followed exertion and disappeared at rest. On the evening of admission, a severe substernal pain which was described as crushing, occurred. It radiated to the right shoulder and down the right arm. The patient vomited twice and had chilly sensations, with perspiration. Her physician gave her an injection of an unknown therapeutic agent, and she was admitted to the hospital 4 hours later.

Physical examination revealed a moderately obese woman in obvious substernal distress. The pulse was 96, and the blood pressure 130/98. The patient was mentally clear but slightly drowsy. The skin was warm and dry. There was no evidence of increased venous pressure in the neck. The lungs were clear to percussion, with some dry inspiratory rales posteriorly at both bases. The apex impulse of the heart was heard at the midclavicular line, and there were no murmurs. The sounds were distant. There was some tenderness in the right upper quadrant of the abdomen. Minimal ankle edema was present. Electrocardiographic records showed changes suggestive of an active process involving the anterior heart surface.

On the following day, the patient developed a complete heart block. The electrocardiographic findings at that time were as follows: auricular rate, 103; ventricular rate, 32–36, with evidence of right bundle-branch block. These findings

were suggestive of anterior infarction, with probable septal involvement. Signs of peripheral vascular failure became evident, and the patient was transferred for study. The blood pressure had fallen from 138/98 to 80/50. The extremities were cold, and there was marked peripheral vasoconstriction. One hour later, the first biochemical studies were made, the blood pressure at that time being 90/70 and varying between this level and 80/50 for the next 6 hours, at which time the second blood samples were collected.

Twenty-four hours after the initial blood was taken, the signs of complete heart block cleared and the blood pressure rose to 100/60. Signs of peripheral vascular failure disappeared. The patient gradually improved and was discharged 9 weeks after entry.

The blood sugar on the initial blood was elevated to 195 mg. per 100 cc. and remained above 150 mg. for the first 6 days (Fig. 3). Following this, the blood-glucose level gradually declined, and on the 24th hospital day it was normal.

The prothrombin time and the icterus index remained normal throughout the hospital stay. With the exception of the blood-glucose level, the biochemical abnormalities referable to carbohydrate metabolism were minimal.

Two of the 12 patients studied (Cases 8 and 10) showed no evidence of peripheral vascular failure. Case 10 was one of probable barbiturate poisoning, and the patient died 12 hours after admission. A complete blood study was made seven and a half hours prior to death. A glucose-tolerance test showed an abnormal tolerance. This was the only biochemical abnormality observed. An interesting phenomenon was the presence of marked fibrinolysis in the blood five and a half hours prior to death.

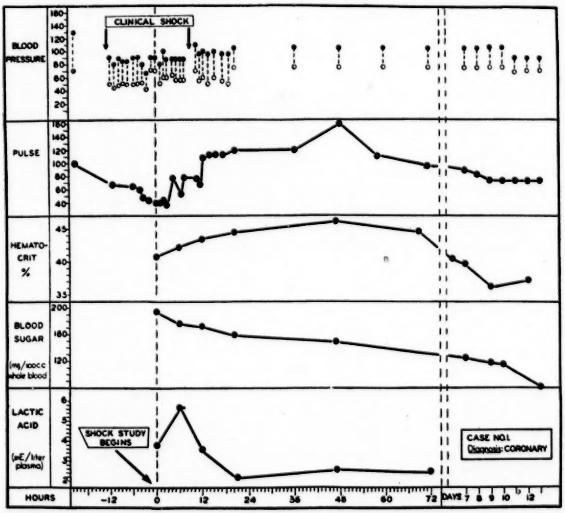

FIGURE 3.

Glucose-tolerance tests were slightly abnormal during the period when hyperglycemia was present. A glucose-tolerance test after discharge was normal, and the fasting blood sugar had been within normal range from the 19th day. Studies of this patient were discontinued on the 24th day.

The plasma lactic acid was 4 milliequiv. per liter on the initial sample, rising to 6 milliequiv. in 6 hours. Thereafter it declined, and at the time of the last sample, 70 hours after the study had commenced, it had reached a level of 2.5 milliequiv. The carbon dioxide combining power remained within normal limits throughout the study.

The nonprotein nitrogen was elevated to 80 mg. per 100 cc. on the initial blood plasma sample and rose to 135 mg. 47 hours later. Seven days later, it had reached a level of 173 mg., and thereafter it slowly declined, reaching 58 mg. on the 24th day after admission. The alpha amino nitrogen showed no statistically significant increase. The urine output during the first 2 days was small but not measured. It was 650 cc. on the 3rd day and gradually increased to normal volume by the 5th day. Single urine specimens had specific gravities ranging from 1.002 to 1.012 during the first 8 days following admission. The sediment showed many white cells and occasional red cells and epithelial cells but no casts.

This blood sample was collected during a period of apnea, which terminated following the administration of oxygen and picrotoxin. The icterus indices of the patients in Cases 8 and 10 were normal, and the prothrombin time in Case 8 was normal.

The patients not described in detail follow similar patterns of response to those outlined above. The clinical manifestations in each case varied considerably, but the biochemical findings differed only in degree.

DISCUSSION

At the outset of this discussion, it must be emphasized that the clinical evaluations were arrived at without reference to the biochemical findings. In the final analysis, the data were arranged according to biochemical findings and the clinical interpreta-

tions were added. Had the reverse procedure been carried out, — namely, an arrangement of the cases on the basis of the degree of involvement with peripheral vascular failure, — the biochemical data would have presented the same pattern as is set forth in this report. The choice of lactic acid levels as the basis for the biochemical arrangement of the data on abnormal carbohydrate metabolism was made because it was the only carbohydrate component that was in no wise directly altered by the necessary therapeutic procedures.

The method of grading the degree of peripheral vascular collapse is quite arbitrary. It is not offered as representing a desirable method, but simply indicates a justification for the classification of peripheral vascular failure used in this presentation. A much larger series of cases would be required to give it greater value. By its use, however, two clinicians were able independently to agree on the status of the clinical material. With the use of these criteria, the data show clearly that there is a high degree of correlation between the existence of peripheral vascular failure and the presence of marked abnormalities in the carbohydrate metabolism of human subjects. This is true regardless of the type of medical illness studied, of which the peripheral vascular failure is a component. Furthermore, on the basis of lactic acid determinations, this small series of patients indicates a close parallel between the degree of peripheral vascular failure and the profoundness of abnormality.

In two cases in which peripheral vascular failure was absent, the disturbance of carbohydrate metabolism was minimal or absent. It is true that consideration must be given to other factors, such as the patient's age and the severity of the illness. The latter is difficult to evaluate, since no patient was studied who was not considered severely ill at the outset. The question of age is more pertinent, since it is known that abnormalities in carbohydrate metabolism occur oftener in the older age groups than in the younger ones. This is notably true in the case of diabetes mellitus.[12] The findings in the 2 cases of presumptive barbituric poisoning (Cases 10 and 11), however, offer some support to the belief that age is not the only determinant. These patients were both in the early thirties, and both had so severe an illness that they died. On the initial blood samples alone, however, the patient in Case 11 had marked disturbance in carbohydrate metabolism, as indicated by hyperglycemia, lactacidemia and acidosis, whereas the patient in Case 10 showed no observable changes in these biochemical findings. The only significant difference between the two patients was that in Case 10 peripheral vascular failure was entirely absent, whereas in Case 11 it was severe and had been present for some length of time. The patient in Case 8, who was nineteen years old, also showed no peripheral vascular failure and only minimal abnormalities in carbohydrate metabolism.

Although such abnormalities in the glucose-tolerance curves showed in the main an intolerance for glucose, many of the curves were not subject to interpretation owing to the rapid and spontaneous fluctuations in glucose at the time of observation. In any event, although abnormalities in glucose tolerance were of the diabetic type, there was no evidence of clinical diabetes in any patient. Furthermore, in the patients who recovered from their illnesses there was evidence of a return of the carbohydrate metabolism to normal. Further follow-up studies will be made and reported later.

Concerning the cause of the abnormality in carbohydrate metabolism, there is no evidence to be drawn from this report. In a previous report some of the most widely accepted theories were reviewed.[6] One may speculate on one contributing factor in these patients. Hematocrit and protein data show that diminution of blood volume although sometimes present was never great and probably could not account for the degree of peripheral vascular failure found. Anoxia is known to produce such biochemical changes as are given here.[13,14] In the production of such an anoxia a reduction in cardiac output may play an important role. On the basis of laboratory and clinical findings, at least three types of anoxia were obviously present in these patients — anoxic anoxia (Case 12), anemic anoxia (Case 3) and presumably stagnant anoxia in the cases with marked cyanosis.

It is of considerable practical importance that femoral venous oxygen determinations give no clue to the state of oxygenation in the tissues in the latter cases. This may well be due to the presence of arteriovenous shunts in the periphery, as first proposed by Cannon[15] and recently postulated by Glenn and his associates.[16] It is significant that oxygen content, saturation and femoral arteriovenous oxygen differences in the few patients studied failed to show a high degree of correlation with the degree of peripheral vascular failure.

That functional disturbances of the liver exist in patients with a marked degree of peripheral vascular failure is inescapable. High icterus indices or prolonged prothrombin times, or both, were present in all patients showing more than the mildest form of peripheral vascular failure, regardless of the disease from which the patient suffered. In some cases the existence of early central necrosis was found in the liver at autopsy.

The alpha amino nitrogen was raised to levels of statistical significance in Cases 3, 5, 7 and 12. In each case there was profound peripheral vascular failure, but in Cases 3, 5, and 12 there was also a strong indication of derangement of liver function. In Case 7, in which there was normal icterus index and no determination of prothrombin time was made, there was evidence of acute degenerative

changes of the liver at autopsy. At the present time the possibility of hepatic function conditioned by decreased hepatic blood flow due to peripheral vascular failure as a cause of the increased alpha amino nitrogen observed in this series cannot be ruled out. The extremely high plasma alpha amino nitrogen in Case 7 (20 mg. per 100 cc.) requires some comment. This patient during the hospital stay had a plasma nonprotein nitrogen greater than 200 mg. per 100 cc. The alpha amino nitrogen of blood plasma is usually 5 per cent of the total nonprotein nitrogen. One might therefore expect in this case that with a normal distribution of the nonprotein constituents of the plasma there would be an increase in the alpha amino nitrogen. It should be noted, however, that following the disappearance of peripheral vascular failure the alpha amino nitrogen fell abruptly from 20 to 10 mg. per 100 cc., at which level it remained until death, although there was no parallel fall in the nonprotein nitrogen.

Azotemia has been found in several of the patients studied. In 1 case it was a serious complication. We[5] have commented previously and elsewhere[17] on the fact that the azotemia found in certain traumatic conditions was due to two components — an increased production of nitrogen and an impaired kidney function. Otherwise we[5] have found a temporary azotemia associated with an oliguria that disappears when the normal urine output is restored. In most cases the azotemia found in the present series was of the latter character. In Case 5, in which the nonprotein nitrogen was over 200 mg. throughout the patient's hospital stay and the signs of uremia were severe and progressive, only a minimal kidney lesion was found macroscopically or microscopically at post-mortem examination. Minor kidney impairment was indicated by urinalysis. In this patient also there is therefore a possibility that the azotemia was in part extrarenal.

The findings in this small series of cases indicate that the biochemical abnormalities accompanying peripheral vascular failure in patients suffering from severe medical illnesses are similar to those found in various traumatic conditions, hemorrhage and anoxia. Although the primordial cause is not known, it is not improbable that when peripheral vascular failure occurs it does so in association with tissue anoxia. Under these circumstances, it is suggested that there is a marked increase in glycogenolysis and possibly gluconeogenesis resulting in hyperglycemia. The production of lactic acid in amounts greater than the liver can transform or greater than can be excreted results in a marked lactacidemia. If there is a concomitant disturbance in hepatic function, as the present data indicate, the lactacidemia may be still further enhanced. Usually, although alpha amino nitrogen is an intermediate in gluconeogenesis, the amount of alpha amino nitrogen formed is easily handled by the normal liver. Alpha amino nitrogen levels in the blood do not ordinarily increase with increases in nitrogen turnover. If, however, as a result of the presence of peripheral vascular failure there is a marked increased protein catabolism, with a failure of deamination due to an impaired liver function, an increase in alpha amino nitrogen is not improbable.

It has been reported that patients with severe medical illnesses may suddenly develop "diabetes" or if previously diabetic may have an exacerbation of their disease.[17] It is not improbable that if the component of peripheral vascular failure is present such observations may represent additional cases of the type of biochemical lesion reported here.

Cardiac infarction has been reported to be accompanied by abnormalities in carbohydrate metabolism of a transitory nature in nondiabetic individuals.[18–20] Eckerström[18] definitely relates the occurrence of such abnormalities to the presence of shock.

Summary

The biochemical changes associated with peripheral vascular failure accompanying severe, acute medical illnesses are described.

They consist of hyperglycemia, lactacidemia and a fall in the bicarbonate reserve. The oxygen saturation of the peripheral blood is reduced. The alpha amino nitrogen of the blood plasma is often elevated. There is usually a lengthening of the prothrombin time, and an elevation of the icterus index.

There is a marked correlation between the degree of the peripheral vascular failure and the profoundness of the biochemical abnormality.

References

1. Clark, E. J., and Rossiter, R. J. Carbohydrate metabolism after burning. *Quart. J. Exper. Physiol.* **32**:279-300, 1944.
2. Clark, E. J., Peters, R. A., and Rossiter, R. J. Nitrogen metabolism after burning. *Quart. J. Exper. Physiol.* **33**:113-127, 1945.
3. Russell, J. A., Long, C. N. H., and Engel, F. L. Biochemical studies on shock: role of peripheral tissues in metabolism of protein and carbohydrate during hemorrhagic shock in rat. *J. Exper. Med.* **79**:1-7, 1944.
4. Hoar, W. S., and Haist, R. E. Amino acid nitrogen changes in shock. *J. Biol. Chem.* **154**:331-338, 1944.
5. Taylor, F. H. L., Levenson, S. M., Davidson, C. S., and Adams, M. A. Abnormal nitrogen metabolism in patients with thermal burns. *New Eng. J. Med.* **229**:855-859, 1943.
6. Taylor, F. H. L., Levenson, S. M., and Adams, M. A. Abnormal carbohydrate metabolism in human thermal burns: preliminary observations. *New Eng. J. Med.* **231**:437-445, 1944.
7. Aub, J. C., and Wu Hsien. Studies in experimental traumatic shock. III. Chemical changes in blood. *Am. J. Physiol.* **54**:416, 1920.
8. Lozner, E. L., Winkler, A. W., Taylor, F. H. L., and Peters, J. P. Intravenous glucose tolerance test. *J. Clin. Investigation* **20**:507-515, 1941.
9. Hamilton, P. B., and Van Slyke, D. D. Gasometric determination of free amino acids in blood filtrates by ninhydrin-carbon dioxide method. *J. Biol. Chem.* **150**:231-250, 1943.
10. Cramer, F. B., Jr., and Winnick, T. Amino acid nitrogen of normal human plasma. *J. Biol. Chem.* **150**:259, 1943.
11. MacFadyen, D. A. Determination of amino acids in plasma by ninhydrin-carbon dioxide reaction without removal of proteins. *J. Biol. Chem.* **145**:387-403, 1942.
12. Joslin, E. P., Root, H. F., White, P., and Marble, A. *The Treatment of Diabetes Mellitus.* 783 pp. Philadelphia: Lea and Febiger, 1940. Pp. 27-34.
13. Kellaway, C. H. Hyperglycaemia of asphyxia and part played therein by suprarenals. *J. Physiol.* **53**:211-235, 1919.

14. VanLiere, E. J. *Anoxia: Its effect on the body.* 269 pp. Chicago: The University of Chicago Press, 1942. Pp. 59-72.
15. Cannon, W. B. *Traumatic Shock.* 201 pp. Chap. 22. New York: D. Appleton & Company, 1923. P. 160.
16. Glenn, W. W. L., Muus, J., and Drinker, C. K. Observations on physiology and biochemistry of quantitative burns. *J. Clin. Investigation* 22:451-460. 1943.
17. Goodpastor, W., Levenson, S. M., Tagnon, H. J., and Taylor, F. H. L. Unpublished data.
18. Eckeratröm, S. Hyperglycémie de type transitoire et glycosurie consécutives à un infarctus du myocarde. *Acta med. Scandinav.* 95: 528-538, 1938.
19. Herrmann, G. Coronary thrombosis and cardiac infarction: clinical presentation, with some remarks upon etiological factors, diagnostic criteria, prognostic data and therapeutic methods. *Internat. Clin.* 3:139-158, 1937.
20. Raab, A. P., and Rabinowitz, M. A. Glycosuria and hyperglycemia in coronary thrombosis. *J. A. M.A.* 106:1705-1708, 1936.

THE EARLY DIAGNOSIS OF PHLEBOTHROMBOSIS*

WILLIAM R. MOSES, M.D.†

WASHINGTON, D. C.

NOTHING so captivates the medical mind as the prevention of catastrophe by a simple method. Thus may be explained the rapidly increasing popularity of proximal ligation of thrombosed veins for the prevention of pulmonary embolism. Indeed, there must be few surgeons who have not witnessed the shockingly sudden transition of a happy convalescent into a patient rapidly dying from this totally unexpected disaster. Nor is the picture of so-called "thromboembolism"[1] infrequent. Neumann[2] in a study of 165 random cadavers, found that 65 per cent of them demonstrated ante-mortem venous thromboses of the lower leg, 52 per cent of which were bilateral. He also stated that 12 per cent of all these thromboses were associated with massive pulmonary embolism and that an additional 34 per cent were associated with multiple nonfatal emboli. Rössle[3] reports that 11 per cent of routine autopsies of patients over twenty years of age showed thromboses of the femoral vein and that 30 per cent of these had developed massive pulmonary embolism. Hosoi[4] attributes 1 death per 1000 hospital population to pulmonary embolus.

Pilcher[5] assigns to embolus 1 death following every 1000 surgical operations. Henderson[6] states that it is the cause of 6 per cent of all postoperative deaths. Allen,[7] quoting Davis of the Massachusetts General Hospital, claims that 3 deaths from embolus followed every 1000 operations. Hunter and his associates[8] attribute 3 per cent of all hospital deaths to pulmonary emboli, and find that 53 per cent of bedridden patients develop deep-vein thrombosis of the legs. McCartney,[9] reviewing over 25,000 autopsies, found 2.7 per cent of the deaths to have been due to emboli in the lungs and estimated that 5.3 per cent of postoperative deaths resulted from this complication. Bancroft[10] expects pulmonary embolism in 10 per cent of victims of phlebothrombosis. Miller and Rogers[11] encountered 7 deaths in 206 patients with clinically recognizable thrombophlebitis.

There thus remains little doubt of both the ubiquity and the seriousness of this condition. At the present time, although there are notable champions of the medical management of these noninflammatory venous thrombi, the greatly preponderant opinion is that proximal ligation, with or without thrombectomy, provides the safest, surest, simplest and cheapest prophylaxis against pulmonary metastasis of the clot.

Regardless of the therapy preferred by the individual physician, however, the selection of cases for treatment rests primarily on the diagnosis of the presence of these thrombi. But establishment of the diagnosis is in itself not at all adequate; the diagnosis must be made at the *earliest possible moment* if the duties of the physician to the patient are to be fully discharged. Welch and Faxon[12] state the problem concisely by asserting that the importance of the diagnosis of deep phlebitis is exactly in reverse ratio to the ease with which it can be made. The surgeon who waits for the full-blown picture of phlebothrombosis, edema of the calf and foot, distended superficial veins, well developed tenderness of the calf and sole, cyanosis of the part, a positive Homans test,[13] a low-grade fever, tachycardia and an increased sedimentation rate will have lost his greatest opportunity to prevent emboli. There of course remain certain patients in whom the first suspicion of venous disease is aroused by an episode of pulmonary embolus. This contingency has been mentioned by Bancroft,[10]; by Allen,[14] who states that chest pain was the first sign in 41 per cent of 202 patients; and by Veal and Hussey,[15] who found that in 10 of 84 patients an embolus was the first factor that drew attention to venous occlusion.

It seems reasonable, however, to predict that the incidence of such unexpected emboli will be substantially reduced by daily or twice-daily inspection of the calves and soles in cases in which the patient's age, the nature of the illness or operation and relative immobilization lead one to expect phlebothrombosis. The examination requires only a few minutes, thus imposing a small price for the prevention of the great majority of these tragedies.

It has been stated that the diagnosis must be made extremely early if the patient is to receive the fullest value of the available procedures. Accordingly, the clinical picture described above must be recognized as the advanced phase of the disease, a phase in which probably the greatest hazard has

*From the Surgical Service, Gallinger Municipal Hospital.
†Chief surgical officer, Gallinger Municipal Hospital.

been passed. Certain minimum standards of early diagnosis must be provided.

In the modern enthusiasm for radiologic diagnosis, the venogram has received ardent support from many students of venous diseases, among them Fine and Sears,[16] Starr, Frank, and Fine,[17] dos Santos,[18] Bauer,[19] Welch, Faxon, and McGahey,[20] DeBakey, Schroeder and Ochsner[21] and Dougherty and Homans.[22] On the other hand, there are many investigators who question the value of venography; these include Bancroft,[10] deTakats[1, 23] and Allen, Linton and Donaldson.[7] It is perhaps significant that some of the advocates of this type of examination in the past have become increasingly more critical in more recent years. Thus, Fine[24] in a recent article shows a considerable decrease of enthusiasm for the procedure. Homans[25] recently called venograms disappointing. Welch and Faxon[23] admit that cases occur in which clinical signs of venous occlusion precede the positive findings of the venogram.

The objections to venography offered by the workers opposed to its use are as follows. There is a definite risk of either initiating or increasing the venous thrombosis. The examination is usually moderately expensive and requires material and apparatus that are not always available. False-negative reports occur in as many as 33 per cent of cases and are especially frequent in the early stages of the disease, when phlebothrombosis is actually most dangerous. There is a large group of venograms in which the interpretation of findings is extremely difficult, especially those of the legs, in which physical signs are minimal — the very cases in which venograms would be most desirable if they were reliable. Lastly, venospasm is frequently impossible to differentiate from organic occlusion. It is probable that a paravertebral sympathetic novocain block preceding the venogram would remove this limitation.

In addition to these objections, there are normally present at least six deep veins of the lower extremity — the paired anterior tibials, the posterior tibials and the peroneal veins. Although venography has been a frequent procedure at this hospital, I have never seen a venogram, either pathologic or normal, in which it was possible to outline these six trunks. If the experience of other observers has been similar, this indicates the extremely limited value of venography in the diagnosis of early phlebothrombosis of the calf veins.

The almost universal acceptance of the sign described by Homans[13] as one of value in diagnosing venous occlusion is subject to some question. Reasoning that this maneuver stimulates too many things at one time, I have had an interesting experience in the last year or so. I have tried this maneuver in 88 patients who had other pathologic conditions not related to phlebitis and in whom phlebothrombosis was not suspected, either at the time of examination or later. This series included 4 patients with contusions of the calf, 6 with fractures of the tibia or fibula, 1 with osteogenic sarcoma of the tibia, 3 with osteomyelitis of the tibia, 2 with septic arthritis of the knee, 2 with septic arthritis of the ankle, 3 with myofasciitis of the calf muscles, 15 with recent ankle sprains, 2 with lacerations of the calf muscles, 1 with a recent penetrating wound of the calf, 4 with recent poliomyelitis, 6 with cellulitis of the subcutaneous tissue of the calf, 5 with various types of acute meningitis, 2 with ruptured intervertebral disks, 4 with "sciatica" of undetermined cause, 7 with peripheral neuritis, 6 with occlusion of the popliteal artery, 1 with scleroderma, 12 adolescents and young adults with ankle fractures whose casts had just been removed, 1 with hysteria and 1 with heat cramps. All these patients demonstrated both limitation of passive dorsiflexion of the ankle and pain in some portion of the calf on performance of this test. Furthermore, none of them subsequently developed emboli or any further local signs compatible with venous occlusion.

Evidence that the incidence of false-negative reactions is high is afforded by Allen's[14] experience, in which only 59 of 202 patients showed Homans's sign in the early phases, although he considers the test as absolutely diagnostic when present — an opinion in which I cannot concur.

In view of the severe limitations of the venogram and the Homans test in the early phase of phlebothrombosis, and the further fact that the classic picture of this malady is actually the late one and is thus valueless in the incipient stage, the question of how one is to make the early diagnosis arises.

It has been noted at this hospital that tenderness of the posterior calf, either localized or extensive and following the course of the deep veins, is almost always the first local sign of venous thrombosis, as has been reported by Veal and Hussey.[15] With the exception of the infrequent cases in which pulmonary embolus precedes local signs of any kind, the stage in which tenderness is the only sign is the ideal time to make the diagnosis and of course to perform a proximal ligation. We see great numbers of such patients owing to the daily examination of the calves of patients whose age, general condition and confinement to bed for long periods make them peculiarly liable to this complication.

Obviously, however, not every patient developing tenderness along the posterior calf has venous disease as the cause. If there were a method of knowing that the tenderness elicited was venous, the diagnosis at this stage would be greatly simplified. In actual practice, pressure along the posterior calf causing pain permits the same diagnostic fallacies as those encountered in the Homans test, because, again, many structures are being simultaneously compressed. The skin, subcutaneous tissue, fascia and large calf muscles are, however, capable of being tested as a group aside from the

deep veins by a simple test. The test employed is as follows.

Firm pressure of the fingers is used to explore for tenderness in any area of the posterior calf (Fig. 1). When the level of tenderness has thus been determined, the calf is firmly compressed from side to side, and the degree of tenderness is compared with that elicited in the first part of the test (Fig. 2). In the presence of bland venous thrombi, the skin, subcutaneous tissue, fascia and muscles show little, if any, tenderness on firm compression, whereas direct pressure on the veins, as executed in the first maneuver, causes definite pain. On the other hand, the superficial tissues are extremely tender at the second test if the tenderness resides in their layers. These two stages do not, however, rule out tenderness of the deep calf nerves, such as is present in a peripheral neuritis. The third part of the test is therefore a brief neurologic examination, with a search for alterations of cutaneous sensation and an evaluation of position sense of the toes, the vibratory sense and the deep reflexes.

FIGURE 1. *The First Maneuver.*
This comprises a careful search for tenderness in the deep posterior calf by direct compression with the fingertips in the anteroposterior direction.

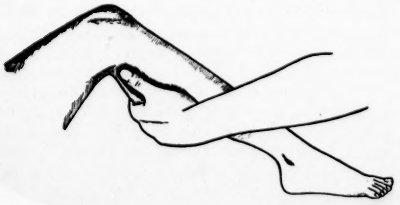

FIGURE 2. *The Second Maneuver.*
The calf is firmly compressed between the fingers and the palm in a lateral direction. In early phlebothrombosis this lateral compression is painless or relatively so, as compared with the first maneuver. The great majority of lesions simulating incipient thrombosis are accompanied by considerable tenderness on lateral compression. The findings in a case of peripheral neuritis, however, may be similar to those in a case of phlebothrombosis; accordingly, a brief neurologic examination of the extremity is included as the third maneuver.

Thus, given a patient in whom tenderness in the calf, either localized or diffuse, is discovered, the suspicion of a deep-vein thrombosis must be entertained. If lateral compression of the belly of the calf at this level is painless or markedly less painful than direct posterior compression, a presumptive diagnosis of phlebothrombosis is indicated. If cutaneous sensation, position sense, vibratory sense and the deep reflexes are then found to be normal, the final diagnosis of phlebothrombosis is warranted.

This test was first used in 12 cases in which thrombi were proved by operative exploration to be present in the venous system of the lower extremity. In each patient the criteria outlined above were exactly satisfied. In 3 cases there was neither pain nor limitation of dorsiflexion on forced passive dorsiflexion of the foot (Homans test). In 2 of 5 patients tested the venogram showed no definite block in either the calf or femoral veins.

Following this experience, proximal venous ligations have been performed at various levels in 59 cases. In 31 of these, phlebothrombosis was diagnosed, the remainder of the ligations being performed for prophylactic purposes, usually in the contralateral legs. In all the 31 cases in which venous occlusion was suspected, the test described above was positive. In 14 of these, a clot was demonstrated by opening the femoral vein or the iliac vein. Of the remaining 17 cases, there was roentgenologic demonstration of pulmonary emboli and infarctions in 12. Since 95 per cent of pulmonary emboli are known to arise in the leg veins, this is strong presumptive evidence of peripheral phlebothrombosis.

In addition to these cases, I have seen 65 other patients in whom incipient phlebothrombosis was suspected. None of these cases yielded the findings described above, and in none was there subsequent evidence of advancing thrombosis, such as emboli, leg edema, cyanosis, venous distention or progressing tenderness. Twenty-six patients, however, showed calf pain on forced dorsiflexion, and 31 presented some degree of limitation of dorsiflexion.

SUMMARY

The high incidence of phlebothrombosis of the leg veins is reviewed, and the lethal potentialities of the condition are discussed.

Considerable stress is placed on the early diagnosis of bland venous thrombi so that methods of prevention of pulmonary embolus may be instituted before the occurrence of this dreaded complication. Detection of these thrombi at this stage requires abandonment of the present dependence on finding the classic picture of thrombophlebitis, because this syndrome represents the late phase of the disease,

the stage in which the greatest risk of pulmonary metastases has passed.

The limitations of venography in making the early diagnosis are discussed. Evidence is also presented that the other great standby, the Homans test, is fraught with certain unavoidable fallacies that result in a dangerously large number of false-positive and negative responses.

A clinical test for the differentiation of early phlebothrombosis and the lesions simulating it is described, and the results of its clinical trial are outlined.

References

1. deTakats, G. Surgical treatment of thrombo-embolism and its sequelae. *Bull. New York Acad. Med.* **20**:623-643, 1944.
2. Neumann, R. Ursprungszentren und Entwicklungsformen der Bein-Thrombose. *Arch. f. Path. Anat.* **301**:708-735, 1938.
3. Rössle, R. Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen. *Arch. f. Path. Anat.* **300**:180-189, 1937.
4. Hosoi, K. Pulmonary embolism and infarction: analysis of 64 verified cases. *Ann. Surg.* **95**:67-92, 1932.
5. Pilcher, R. Pulmonary embolism: statistical investigation of its incidence in 12 London hospitals in decade 1925-34. *Brit. J. Surg.* **25**: 42-56, 1937.
6. Henderson, E. F. Fatal pulmonary embolus: statistical review. *Arch. Surg.* **15**:231-236, 1927.
7. Allen, A. W., Linton, R. R., and Donaldson, G. A. Thrombosis and embolism: review of 202 patients treated by femoral vein interruption. *Ann. Surg.* **118**:728-740, 1943.
8. Hunter, W. C., Krygier, J. J., Kennedy, J. C., and Sneeden, V. D. Etiology and prevention of thrombosis of deep leg veins: study of 400 cases. *Surgery* **17**:178-190, 1945.
9. McCartney, J. S. Postoperative pulmonary embolism. *Surgery* **17**: 191-206, 1945.
10. Bancroft, F. W. Phlebothrombosis of femoral and iliac veins. *S. Clin. North America* **25**:325-333, 1945.
11. Miller, R. H., and Rogers, H. Postoperative embolism and phlebitis. *J. A. M. A.* **93**:1452-1456, 1929.
12. Welch, C. E., and Faxon, H. H. Thrombophlebitis and pulmonary embolism. *J. A. M. A.* **117**:1502-1508, 1941.
13. Homans, J. Exploration and division of femoral and iliac veins in treatment of thrombophlebitis of leg. *New Eng. J. Med.* **224**: 179-186, 1941.
14. Allen, A. W. Thrombophlebitis and pulmonary embolism. *Kentucky M. J.* **42**:160-165, 1944.
15. Veal, J. R., and Hussey, H. H. Surgery of deep vein thrombosis of lower extremity. *Surgery* **17**:218-231, 1945.
16. Fine, J., and Sears, J. B. Prophylaxis of pulmonary embolism by division of femoral vein. *Ann. Surg.* **114**:801-812, 1941.
17. Starr, A., Frank, H. A., and Fine, J. Venographic diagnosis of thrombophlebitis of lower extremities. *J. A. M. A.* **118**:1192-1195, 1942.
18. dos Santos, J. C. La phlébographie directe. *J. int. de chirurgie* **3**: 625-669, 1938.
19. Bauer, G. Venographic study of thromboembolic problems. *Acta chir. Scandinav.* Supp. **61**, 1940.
20. Welch, C. E., Faxon, H. H., and McGahey, C. E. Application of phlebography to therapy of thrombosis and embolism. *Surgery* **12**: 163-183, 1942.
21. DeBakey, M. E., Schroeder, G. F., and Ochsner, A. Significance of phlebography in phlebothrombosis. *J. A. M. A.* **123**:738-744, 1943.
22. Dougherty, J., and Homans, J. Venography: clinical study. *Surg., Gynec. & Obst.* **71**:697-702, 1940.
23. deTakats, G., and Fowler, E. F. Problem of thrombo-embolism. *Surgery* **17**:153-177, 1945.
24. Fine, J., and Starr, A. Surgical therapy of thrombosis of deep veins of lower extremities. *Surgery* **17**:232-239, 1945.
25. Homans, J. Diseases of veins. *New Eng. J. Med.* **231**:51-60, 1944.

THE REGIONAL INJECTION OF PENICILLIN IN LOCAL INFECTIONS

A Preliminary Report

DAVID ROSE, M.D.,* AND DAVID HURWITZ, M.D.†

BOSTON

THE advent of penicillin has opened up innumerable fields of exploration in the treatment of infection. Sufficient work has been done and enough reports have been published on the production, assaying and pharmacology of the drug to permit omission of their discussion. This report is mainly concerned with the administration and dosage of penicillin in local infections, with direct regional injection and without systemic injections or other local therapy.

There have been many attempts to use penicillin locally. Peck[1] reported 15 cases in which this drug was employed locally with good results. He, however, also used it systemically, and in some cases in combination with sulfonamides and local treatment consisting of x-ray and incision. The local use consisted of injection into the necrotic mass or a sinus and prevention of drainage by occlusion with adhesive tape. These treatments were often repeated every three hours, each dose consisting of 100 to 1000 units. Florey[2] recommended the use of penicillin locally. He found it best to establish a closed cavity when possible, into which penicillin could be instilled and from which exudate could if necessary be sucked periodically. Cutler[3] advocated penicillin mixed with dehydrated human plasma and applied with a powder insufflator. Sophian[4] recommended an ointment containing penicillin for topical application for furunculosis and similar infections. Flippen[5] states that penicillin may be injected into a localized abscess cavity after aspiration of pus. He warns against the spread of infection by the purely mechanical means of distending firm areas of cellulitis, which we have proved in our series to be an unnecessary cause for alarm. Poate[6] advocates the use of penicillin in solution, introduced through a fine tube into wounds, and as a powder, which is sprayed. Fisher[7] reported 95 cases treated by instillation and irrigation, in which the lesion was either open or well drained.

The present report is a preliminary one on the use of penicillin by direct injection into the infected tissues. This method is in contradistinction to so-called "injections" that are actually instillations into sinus tracts or cavities, the drug being retained by occlusion of the tract opening by adhesive tape or other means. In this series, the penicillin was injected hypodermically, the size and length of the needle varying with the type and size of lesion treated. The best results were obtained by injecting well outside the involved area and directing the

*Associate visiting surgeon, Cambridge Hospital, and senior visiting surgeon, Cahill House, Cambridge City Hospital.

†Associate visiting physician, Cambridge Hospital.

needle toward the center of the infected site, and by outlining the injection zone not by the visible cellulitis but by the zone of tenderness to palpation. The latter is often 0.5 to 1.0 cm. beyond the outermost margin of redness in apparently uninvolved tissue. The rationale of this approach lies in an attempt to augment and reinforce the barrier that the body tissues set up to localize the spread of infection. Injection outside of and through the natural barrier to the center of infection thus aids the body reaction not only in preventing spread of infection but also in combating the infected tissue. This is a highly important phase in the administration of penicillin for regional use. Direct injection into the infected mass, although of value, does not produce so rapid and truly spectacular results as does the method described above. In addition to outlining the zone of tenderness, we have divided the area into three or four sections for injection.

In this series, injections were given once daily and the dosage was worked out for each case by virtue of the type, location and extent of infection. No case received solutions containing less than 15,000 units per cubic centimeter, and some received those containing as much as 60,000 units per cubic centimeter. In relation to dosage, there are two factors for consideration: — the total volume and the number of units per cubic centimeter. In the first few cases treated, we hesitantly used solutions containing 15,000 units per cubic centimeter and divided the amount injected into two to four parts, depending on the number of sites. As the work progressed, it was found that the concentration could be increased without untoward results. The volume, however, is definitely limited by the site of infection. For example, in cases of felon or paronychia it is difficult to use a large volume; on the other hand, in cases of carbuncles or cellulitis, where there is considerable fatty and areolar space tissue, large volume can be employed.

Several general observations were made. Injections in fingers and hands are painful. This is apparently due more to the volume injected than to the concentration, since high concentrations in small volume were not much more painful than larger but more dilute volumes. Novocain nerve block was tried with some patients, but they complained as much of the block as they did of the penicillin injection. In 1 case, nitrous oxide and oxygen anesthesia was used to permit a high concentration in a felon. Intravenous Pentothal Sodium was employed in a case of bilateral felon. In all cases, within one to four hours after the initial injection the affected part became almost completely free of pain and could be actively used, and palpable tenderness was minimal. In all cases, the area treated became reddened and later mildly cyanotic, the latter condition persisting long after the infection had cleared up. In most cases desquamation of the skin took place after healing, but in some it occurred during the healing process. There was no toxic reaction, and no sloughing of tissues.

In many cases in which pus formation had become established, spontaneous evacuation occurred during or after the second treatment. In some cases the pus was completely absorbed without evacuation. This brings up the question of desirability of evacuation of pus by needling or even by incision. During the first few treatments it was thought desirable to maintain a closed system so that the penicillin would be kept in contact with the pathogens and tissues more completely and for a longer period of time. It was also found that in the cases with a collection of pus near the surface it spontaneously evacuated during an injection or shortly thereafter. In some cases the pus was evacuated by needle after the initial treatment. For these reasons, we have not employed incision and drainage, and the lesions have responded just as well to treatment without them. This may seem contrary to one of the basic rules of surgical treatment, namely that evacuation of an enclosed pus pocket is the only correct treatment. Although this has been true up to the present, it now appears possible not only to limit the infection but also to overcome it without deforming incisions and with a marked decrease in disability, pain and length of hospitalization. It must, however, be kept in mind that this treatment does not preclude surgery in some cases. Judgment must be exercised in deciding whether the process of healing may be hastened by evacuation of the pus rather than by absorption. In such a case, evacuation by incision or needling can be done, but only after treatment by injection has abated the acute process and complete localization has been attained. To date, there have been only a few cases in which evacuation was done by needling and only 1 in which it was done by incision; in several cases the lesion had been incised previous to admission to the hospital.

In practically all cases, the systemic use of penicillin or sulfonamide therapy was excluded and no x-ray or other local therapy was employed.

Method of Use

Penicillin dissolved in saline solution was prepared in the usual manner, the amount of saline used depending on the type and size of lesion to be treated. In fingers and other areas where loose tissue precluded a large volume, 2 to 4 cc. was used to dissolve 100,000 units of penicillin, thus giving a concentration of 50,000 to 25,000 units per cubic centimeter. The parts were cleansed with soap and water and painted with an aqueous solution or tincture of Zephyran, and zones of tenderness mapped out. Whenever possible, two to four sites of injection were chosen. In all cases, the injection was made by hypodermic needle, starting outside the zone of palpable tenderness, injecting slowly ahead

of the needle and progressing toward the center of the infection. The injection was made deeply in the tissue, not merely subcutaneously, except in cases in which the infection was within the skin, such as furuncles. A sterile needle was used for each injection site.

On the following day the lesion was examined and again injected. The dosage and volume were determined in relation to the progress of abatement of infection, and this procedure was continued until infection was completely controlled. A dry dressing was applied and was changed as needed if any discharge was present.

Results

This series comprised 2 cases of osteomyelitis of the finger, 6 of felon, 6 of carbuncle, 3 of perianal infections, 6 of cellulitis, with and without abscess, and 2 of furuncle. Table 1 shows the types of infection, complications, dosage and so forth.

A few cases are worthy of discussion as illustrating the treatment and the results obtained.

Osteomyelitis

Case 1. L. J., a 36-year-old housewife, was a known diabetic patient who had neglected her treatment for 2 years. Twelve days prior to admission, she sustained a puncture wound of the right middle finger. This became infected and was seen by a local physician, who treated it by hot soaks and later by a small incision on the palmar surface at the tip. The finger became progressively worse, and on February 6, 1945, the patient was admitted to the Cambridge Hospital by one of us (D. H.), who had originally treated her diabetes. He found the diabetes uncontrolled and undertook its management. The finger was incised under general anesthesia and the pus was evacuated. Sloughing down to the distal phalanx was found. Cultures revealed *Staphylococcus aureus*. X-ray examination revealed osteomyelitis. The systemic use of penicillin, 120,000 units every twenty-four hours in divided doses every three hours, was instituted. This dosage was increased to 150,000 units every twenty-four hours and maintained for 8 days. During that time, the finger became progressively worse. There was a dusky, bluish swelling of the entire finger, with severe, constant pain and moderate discharge of pus. On February 13, two injections of penicillin, each of 15,000 units in 1 cc. of solution, were made at the base of the finger on the medial and lateral sides toward the tip of the finger. On the following day, the patient was free of pain for the first time and the color and swelling of the finger had markedly improved. The same dosage and volume were employed daily, with the injections made closer and closer to the tip of the finger, the last three being made directly into the localized area of osteomyelitis. On February 19, 6 days after the local injections, the finger was of normal size and color. Motion was free, there was no pain or tenderness, and the discharge of pus had ceased. X-ray films showed slight improvement in the osteomyelitis. The penicillin was stopped, and on February 24 the patient was discharged. The diabetes was practically controlled. Two weeks later, the finger was healed. There was no sequestrum.

This was the first case of any sort in which direct injection of penicillin into a local infection was employed. A subsequent case (Case 2) was treated earlier and more vigorously without systemic penicillin, and as good a result was obtained as in Case 1.

Felons

Felons need no special discussion, since Table 1 is self-explanatory, but one case merits brief mention.

Case 7. E. R., a 34-year-old female, was referred with felons of both thumbs. The left thumb, which had been incised and drained 7 days previously, was still painful and swollen and was draining freely. The right thumb was acutely infected and was tender, reddened and swollen. Under intravenous Pentothal Sodium anesthesia both thumbs were cleansed and painted. One hundred thousand units of penicillin was dissolved in 2 cc. of saline solution, and 1 cc. was injected into the left thumb below the depth of the incision. The remainder of the solution, with a fresh needle, was injected into the right thumb at two puncture sites. On the following day, the right thumb was needled and drainage of pus was obtained. No further treatment was instituted, and both thumbs promptly healed.

Carbuncles

The carbuncles demonstrated a marked and even spectacular response to direct-injection therapy. None of these cases had incision or even separation of bridges between cavitations. In 1 (Case 9), the carbuncle had been incised and drained a week before the patient reached our hands. It is of interest that this patient received more treatments (seven) with a greater total dosage of penicillin (495,000 units) than did those whose carbuncles had not been incised. In all these cases there was spontaneous evacuation of pus and separation of slough within two to five days after the onset of treatment. In some cases in the early stages of treatment heat was applied in the form of poultices or moist dressings. Later the use of heat was abandoned. All the patients were ambulatory following the first treatment. Two cases deserve explanation.

Case 10. H. C., a 47-year-old, married woman, was admitted to the Cambridge Hospital on March 28, 1945, after having been seen at home in consultation. There was a carbuncle on the lateroanterior aspect of the neck, overlying the large vessels. Its dome was 7 cm. in diameter, with multiple oozing sinus points. The base measured 15 cm. in diameter and extended down to the clavicle. The skin was reddened and burnt, with a vesiculation, as a result of too vigorous heat therapy before a physician was called. The temperature on admission was 102.4°F., and the pulse 100. The white-cell count was 15,400 and a culture revealed *Staph. albus*. Four cubic centimeters of penicillin, 20,000 units per cubic centimeter, was injected, with four sites of injection. Fifteen minutes after treatment, the patient was able to move her head and felt much more comfortable. On the following day, the area of redness and edema was markedly decreased and only moderately tender. One cubic centimeter of solution containing 30,000 units of penicillin per cubic centimeter was injected at each of four sites, which approached the center of the carbuncle. On the 3rd day the same dosage was employed, and later that day the slough was lifted out *en masse*. No further treatment was given, and 2 days later the patient was discharged home with a practically dry wound. It was completely healed within 10 days.

In this case, the location, size and poor condition of the surrounding skin was such as to make extensive incision and drainage a risky procedure.

Case 11. B. M., a 43-year-old man with a carbuncle of the left temple, was being treated by penicillin systemically and heat locally when his case came to our attention. The blood sugar was 111 mg. per 100 cc. A blood culture was negative, and a local culture was not obtained because there was no discharging pus but only multiple points heading up. On May 11, 1945, 40,000 units of penicillin was given intramuscularly in divided doses, and on May 12, 120,000 units was given. Following this, local treatment was advised and 20,000 units of penicillin in 1 cc. of solution was injected at each of four sites. On the following day, there was a soft,

TABLE 1. *Summary of Data.*

Case No.	Age	Sex	Diagnosis	Associated Disease	Concentration	Volume	Frequency of Treatment	Treatments	Total	Other Treatment	Result
	yr.				units/cc.	cc.			units		
1	36	F	Osteomyelitis of finger	Diabetes	15,000	2	Once daily	7	210,000	Incision and drainage on admission; 125,000 units of penicillin systemically for 10 days, without results; treatment of diabetes.	Complete healing; no sequestrum.
2	40	F	Osteomyelitis of finger	None	30,000	2	Once daily	7	420,000	Incision and drainage 2 weeks before treatment	Complete healing; no sequestrum
3	18	F	Felon of finger	None	30,000	1	—	1	30,000	None	Absorption; no drainage.
4	19	F	Felon of finger	None	20,000	1	Once daily	3	60,000	None	Absorption; no drainage.
5	21	F	Felon of finger	None	40,000 20,000	2 1	Once daily Once daily	1 1	100,000	Pus evacuated by needle day after first treatment	Complete healing
6	21	F	Felon of finger	None	40,000	2	Once daily	3	240,000	Needling 2nd day; no pus obtained.	Complete healing; spontaneous drainage 3rd day.
7	34	F	Felon of left thumb	None	50,000	1	—	1	50,000	Incision 7 days before admission	All drainage ceased after treatment; healed.
			Felon of right thumb	None	50,000	1	—	1	50,000	Needled day after treatment	Complete healing; drainage of pus following needling.
8	47	M	Carbuncle of neck	None	30,000	3	Once daily	5	450,000	None	Spontaneous sloughing; complete healing.
9	60	F	Carbuncle of neck	None	15,000 30,000	3 3	Once daily Once daily	3 4	495,000	Incision and drainage before admission	Drainage and absorption; complete healing.
10	47	F	Carbuncle of neck	None	20,000 30,000	4 2	— Once daily	1 2	200,000	None	Slough lifted out *en masse* after third treatment; complete healing.
11	43	M	Carbuncle of left temple	None	20,000	4	—	1	80,000	Systemic penicillin: 40,000 and 120,000 units before local treatment, and 100,000 units after local treatment.	Following local treatment, edema and erythema extending into eye and cheek; next day, spontaneous evacuation of slough, with rapid recovery.
12	48	M	Carbuncle of neck	None	40,000 25,000	2½ 4	— —	1 1	200,000	60,000 units of penicillin systemically	Spontaneous evacuation 2nd day after treatment; complete healing.
13	40	M	Carbuncle of left shoulder	None	40,000 45,000	2½ 4	— Once daily	1 4	820,000	None	Slough partially removed 2nd day; completely removed 5th day; complete healing.
14	13	F	Perianal abscess	Fistula and diabetes	20,000 40,000 20,000	5 3 5	Once daily Once every 5 days Once every 3 days	7 3 2	1,260,000	Treatment of diabetes	Complete healing of tract internally and externally
15	42	M	Perianal abscess (anterior)	Anterior fistula	10,000	4	Once daily	3	120,000	None	Spontaneous evacuation and healing of abscess
16	36	M	Draining perianal abscess (posterior)	Posterior fistula	12,500	2	—	1	25,000	None	Abscess dry 2 days after treatment
17	29	F	Cellulitis of palm	None	10,000	2	—	1	20,000	None	Absorbed completely; no drainage.
18	29	F	Cellulitis of base of thumb	None	10,000	2	Once daily	4	80,000	None	Absorbed; no drainage.
19	21	M	Cellulitis of right knee (foreign body)	Diabetes	20,000	2	Once daily	3	120,000	None	Spontaneous drainage after first treatment
20	41	M	Cellulitis of left middle finger, with tenosynovitis	None	50,000	2	Once daily	2	200,000	Sulfonamide treatment for 2½ weeks before admission	Complete absorption; residual stiff finger.
21	26	M	Cellulitis with palmar abscess	None	20,800	2	Once daily	2	80,000	Needled for evacuation of pus	Complete healing
22	41	M	Cellulitis with palmar abscess	None	50,000	2	Once daily	3	300,000	Incised for evacuation of pus on 3rd day	Rapid healing
23	18	F	Furuncle of neck	None	20,000	1	—	1	20,000	None	Spontaneous drainage day after treatment
24	18	F	Furuncle of neck	None	40,000	1	—	1	40,000	None	Spontaneous drainage on day of treatment

erythematous edema about the upper face, extending into the eye and cheek of the affected side. Because of this, the local treatment was omitted by the attending physician, and 100,000 units was given systemically. On the following day, there was spontaneous drainage and separation of slough, which was lifted out. There were no further treatments, and 3 days later the lesion was practically healed.

This was the only case in which a local reaction was observed.

Anal Infections

The only comment that can be made concerning the use of penicillin in anal infections, until a larger number of cases are studied, is that local therapy cleans abscesses preparatory to surgical removal of fistulas. In Case 14, the fistula healed completely internally and externally and no later surgery was necessary.

Cellulitis

Cellulitis, with or without abscess formation, responds favorably to this mode of therapy. In fact, regional injections are of the utmost importance in limiting and localizing the spread of infection. In our 6 cases, there were 3 that never progressed to abscess formation. One case drained spontaneously, in 1 the pus was evacuated by needling, and had a small superficial incision for drainage. All these infections became localized in one to three days after onset of treatment. One case stands out as an example.

Case 20. J. G., a 41-year-old man, sustained a minor laceration over the palmar surface of the proximal phalanx of the left middle finger. Twenty-four hours later, the finger was twice its normal size, reddened and painful. A physician advised hot soaks and 1 gm. of sulfathiazole thrice daily. After 3 days, an attempt to reopen the laceration, which had closed over, was made, but no pus was obtained. The same treatment was continued for 2 weeks, during which time the hand became worse. At the end of 3 weeks, when we saw the hand, there was a hard, brawny cellulitis involving the entire middle finger and the proximal portions of the two adjacent fingers, with a softer edema of the entire dorsum and palm of the hand. The finger was cyanotic and in stiff extension. It was tender and the site of a throbbing pain. There was general malaise but no fever. An immediate injection of 100,000 units of penicillin in 2 cc. of solution was made. The sites elected were lateral and medial to the initial laceration, using 1 cc. for each site and directing the needle deeply to the palmar fascia. On the following day, the palmar surface of the hand was only slightly swollen. The palmar surface of the finger was swollen but soft and nontender and its color was nearer normal. Its dorsal surface was still cyanotic, swollen and tender. This time the injection, with the same dosage and the same concentration, was made from the medial and lateral surfaces toward the dorsum. On the following day, the entire finger was normal in color, although with a soft swelling. There was no pain or tenderness. The palm was free of swelling, but there was a slight amount of soft swelling of the dorsum of the hand. The patient stated that he had had the first night of complete freedom from pain since the onset of infection. The finger was still stiff and could not be flexed. Without further therapy other than hot soaks, all swelling disappeared. Although some inability to flex is still present, slow improvement has continued.

Furuncles

No comment is needed concerning furuncles, since these are relatively simple infections. They respond well. Usually one injection in the surrounding zone or under the base of the lesion is sufficient for complete relief and healing.

* * *

Cultures of all lesions were made when pus was present. The organisms found were either *Staph. aureus* or *Staph. albus*, except for Case 14, which showed *Streptococcus haemolyticus*.

The results were extremely gratifying. No deforming surgery was done. Evacuation of pus, when formed, was usually obtained by spontaneous evacuation or needling. There were no cases of sloughing, tissue necrosis or dissemination of infection. The reduction of disability (Table 2) and rapidity of healing are in favorable contrast to the results of orthodox surgical treatment.

Table 2. *Duration of Disability.*

Diagnosis	Shortest Period	Longest Period	Average Period
	days	*days*	*days*
Carbuncles	4	14	7
Osteomyelitis	14	32	23
Felon	0	3	2
Cellulitis	0	7	4

Summary and Conclusions

Penicillin employed by direct injection is of definite value in limiting and overcoming local infections.

Concentrations of penicillin as high as 60,000 units per cubic centimeter may be used without complications. One of the values of direct injection is the ability it gives to produce a high local concentration, which is impossible by systemic use of the drug.

Disability is reduced far below the point reached by any other means of treatment.

There is no deformity such as that frequently following radical surgical incision and drainage.

Pain is quickly relieved — in some cases within one hour, and always within thirty-six hours.

Surgical judgment must be exercised regarding the necessity and proper time for evacuation. Preferably, no evacuation should be performed until complete localization by injection therapy has been carried out, and then only minimal surgery is indicated. Most cases evacuate spontaneously during localization, with freedom from pain.

Injections are painful, and the degree of pain is in direct ratio to the density of tissue and the volume of injection.

Injections once daily are adequate, but they must be maintained until definite subsidence of infection is evident.

The fear of spreading the infection by this treatment has not been substantiated. In part, this is due to the fact that injections are started well outside the center of infection, thus reinforcing the barrier and aiding in localization.

We are indebted to Dr. Samuel M. Perlmutter and Dr. Leo A. Blacklow for the data on their patients included in this series.

REFERENCES

1. Peck, F. B. Penicillin with special reference to its use in infections complicating diabetes. *Am. J. M. Sc.* **208**:581-596, 1944.
2. Florey, M. E., and Florey, H. W. General and local administration of penicillin. *Lancet* **1**:387-397, 1943.
3. Cutler, E. C., and Sandusky, W. R. Method for local administration of penicillin. *Surgery* **16**:937, 1944.
4. Sophian, L. H., and Connolly, V. J. Use of penicillin in topical application. *Am. J. M. Sc.* **208**:577-580, 1944.
5. Flippen, H. F. Penicillin therapy. *Delaware State M. J.* **17**:37-41, 1945.
6. Poate, H. R. G. Local use of sulphonamides and penicillin. *M. J. Australia* **1**:6-9, 1945.
7. Fisher, A. M. Therapeutic value of penicillin applied locally, based on experience with crude material in variety of infections. *Bull. Johns Hopkins Hosp.* **76**:134-153, 1945.

SYMPOSIUM ON MEDICAL SOCIOLOGY

PRACTICAL CONSIDERATIONS IN THE PLANNING AND CONDUCT OF A NATIONAL MEDICAL-CARE PROGRAM*

EDWARD S. ROGERS, M.D.†

DURING the course of the preceding few weeks you have had laid before you an exceptionally well chosen review of facts, attitudes and plans with respect to the problem of medicine and its place in a changing social structure. Regardless of the details of the views that you have formulated, there probably are few, if any, of you who will not agree that fundamental changes are in motion.

Medicine as a science has been through, and is still in, a most amazing period of progress. We need not review the evidence here. Similarly, other forces of great moment to the social structure have been through periods of growth. Transportation provides a good example. Its growth and its new horizons have had far-reaching effects on our way of living. It seems just as fallacious to adhere to the concept that the advances in medicine will not have their counterpart in changes in the former patterns of medical practice — our manner of living with respect to the use and distribution of medical services — as it would be to claim that modern transport has not brought and will not continue to bring changes in the country's standards and manner of living.

These changes are not "around the corner." They are here today and will be even more so tomorrow. Let anyone who doubts this but take the trouble to review the major party programs in the last presidential campaign. Advances in social security, you will recall, were not an issue challenged by either, and medical care is recognized as an important part of social security.

Regardless of the justifiable pride that we all enjoy in the past achievements of the medical profession, regardless of the high quality of the national health and regardless of the apprehensions that beset many in our ranks and make them shut their eyes, the facts in proof of the imperfections of the present system of medical services are clear. I therefore believe that change is not to be feared but rather to be sought.

The facts have been ably pointed out to you in previous lectures, and you know them as facts, but how deeply do you feel them? Some of you may have experienced them at first hand; most of you probably have not. You do not see people seriously lacking for medical facilities here. The social implications of failures in preventive practice are not readily observed in the laboratory, the clinic or the classroom, although they are of course basic and are in the background. You are not exposed to poor medicine in the cloisters of this school, and you are not being prepared to practice it. But neither the world nor the Nation begins and ends in Boston with both feet in these buildings, as I used to think.

I have sat in the seats you occupy, and, like you, I have been inspired; and I have also been put to sleep. I am not stirred by any unusual sense of school patriotism, but I have always been proud to have graduated from these halls, because to have done so has numbered me, as it will you, among men well trained and with a high tradition, from among whom many of the leaders of this profession have risen. Never before has the medical profession stood in greater need of sane, clear-thinking leadership, both now and in the years immediately before us, and these years will be the years of your increasing responsibility. That is why I say that you know these facts but question how deeply you feel them.

I have said that the need is great and that you will have much to do in determining the future. I shall attempt to show you why.

In the light of your studies and discussions, probably each of you has either formulated or is formulating your own plan, your own concept of the solution of the problem of medical care. The many and various patterns of such concepts will reflect a variety of molding forces, such as your awareness of need, your experience, your type of information and interest, your intellectual methods and, by no means the least, your basic prejudices. Yes, you

*This is the ninth and concluding of a series of nine lectures on medical sociology given weekly at Harvard Medical School during January, February and March, 1945; they were sponsored by the Department of Preventive Medicine and were primarily intended for third-year students. These articles have temporarily replaced the reports "Medical Progress."

†Assistant commissioner for medical administration, New York State Department of Health; assistant professor of medicine, Albany Medical College.

have them, — all of you, — and you have the most, in all probability, when you fail to recognize them.

In these respects you do not differ greatly from those in whose hands the delicate buds of the future of medicine lie today. To be sure, most of these men have had from a few to many years of experience, and some of them, thank heaven, are real leaders, rich in their ability to evaluate the forces in their own thinking and to recognize the merit in another's point of view. Many, however, are not so. They have had what should be rich experience, but they take a sort of polaroid point of view toward it and see only the things that are in parallel with their prejudices.

I have mentioned the formulation of a plan. This is essential if we wish to end our present more or less haphazard practices and move effectively toward an objective. I shall, however, be but little concerned with other than the broadest aspects of planning today, because what I have to say will apply equally to any plan. It is essentially this: your plan, my plan, the Surgeon General's plan or the President's plan will be no better than its chances of actually accomplishing its objectives.

Plans that purport to answer one phase or another of the problem of medical care are of frequent occurrence these days, and there are about as many variations as there are groups contributing them. Many of these plans have been in operation over a period of years. Especially is this true in other countries. By and large, however, with the exception of Russia, these programs, like those in operation in this country, fall short either of being comprehensive or of covering the entire population. And, as Dr. Goldmann[1] doubtless advised you in his lecture, one must be circumspect in the matter of applying the experiences of other nations, with political and social structures so different from ours, as a pattern for our actions.

In this country one finds rapidly growing movements such as hospital insurance under Blue Cross systems, a large variety of voluntary medical and medical-indemnity insurance schemes for the low-income and certain industrial groups and a small but increasing number of fairly comprehensive hospitalization and medical-care plans for the indigent. But none of them, so far as I am aware, embrace comprehensive provisions for health and preventive services and for the improvement of the quality and distribution of medical services for other than limited segments of the population. Nor have they been developed as a part of a planned master strategy that envisions the way they fit into a total program of medical care.

Even in the area of national planning, it seems to me that there has been either too much opportunism or too little regard for sound basic principles, as in the Wagner–Murray–Dingell Bill of 1944. The hospital-construction bill (S-191) of Senators Hill and Burton, now before Congress, impresses me as being much more realistic, and although it is not comprehensive in the terms of the whole problem, it nevertheless suggests that its authors have a pretty clear concept of how it would fit as a part of a rational master plan.

Among the comprehensive programs recommended by national organizations, that of the American Public Health Association[2] merits attention because it is clear, comprehensive and comparatively simple. Although it achieves this clarity and simplicity by the expedient of confining itself to a statement of a few objectives and principles applicable to method, it does so, of course, at the cost of begging a great many major problems of detail in technic. I am rather of the opinion that this is wise in national planning at this stage, but from the practical point of view of a person who wants to know exactly what he should do as a physician or an administrator, it is not of much help. We must start somewhere, however, and we must have some common ground of agreement regarding where we want to go. Such a common ground, when clearly stated and properly implemented with principles for our guidance, constitutes a master plan in the sense that I am using the term. Not to have such a plan would be analogous to trying to fight the present war without a master strategy. Yet the present lack of basic master planning and agreement in the war on the medical and health needs of the country is of this order.

You cannot escape your present and increasing responsibility and concern in this problem. You cannot evade it today as citizens. You should not evade it tomorrow as physicians. And some of you, I hope, will assume roles of leadership with respect to it in the years that lie ahead. It is not a problem that will be solved with the mere passage of a bill or two.

Accordingly, I want to discuss with you certain points of view and problems that may serve as guides to your thinking in relation to your responsibilities as citizens, physicians and potential leaders among physicians.

First of all, you should establish a set of values with which to measure this business of planning, and second, you ought to attain some insight concerning the practical problems of accomplishing a plan once it is accepted.

What are the fundamentals of a master plan? I can speak only for myself, of course, but to me it seems that such a plan should embrace the following characteristics. It must be clear as to its objectives, and these must be comprehensive in nature. It must be practical and make provision for the logical steps by which it is to be developed. It must meet the needs of and be acceptable to those whom it most greatly affects. It must contain the substance for authority, responsibility and orderly administration. Lastly, it must be flexible with respect to local situations and future developments.

The foregoing principles, platitudinous-sounding and perhaps overly concise, have not been lightly written. In them I have endeavored to include those elements of a plan that will determine whether or not it is realistic and capable of accomplishment. It will be worth while to consider each of these principles in more detail, both as abstract principles and in the light of current experience.

The plan must be clear as to its objectives, and these must be comprehensive in nature. Although we have achieved no single statement of national objectives in a formal sense, we are not far from it, and we can almost check this off as finished. For example, very few people will take serious exception to the objectives for a national medical-care and health program set forth by the American Public Health Association[2] in December, 1944, which read as follows:

1. A national program for medical care should make available to the entire population all essential preventive, diagnostic and curative services.
2. Such a program should insure that the services provided be of the highest standard, and that they be rendered under conditions satisfactory both to the public and to the professions.
3. Such a program should include the constant evaluation of practices and the extension of scientific knowledge.

Compare these with the following seven principles recently announced by the Council on Medical Service of the American Medical Association.[3]

1. Continued expansion of the practice of medicine with full development of approved voluntary hospital, medical, indemnity, industrial and commercial insurance against the costs of medical care.
2. Development of public-health facilities for preventive medicine all over the country.
3. Development of adequate diagnostic facilities everywhere.
4. The use of the voluntary-insurance principle in caring for the indigent and medically indigent.
5. The development of hospital facilities where present facilities are used to the utmost and are still inadequate.
6. The use of federal funds to aid communities in public-health measures, care of the indigent and construction of necessary hospitals, when local communities are unable to finance the projects, but with the retention of local administration.
7. The creation of a unified federal Department of Health, with a secretary in the Cabinet as the head of the department, such secretary to be a qualified physician.

Although I prefer the form of the American Public Health Association's statement, which is natural, since I had a part in its formulation, there are quite a few points of similarity in these two sets of objectives. Of course, those of the American Medical Association are not statements of pure objective, being intermixed with recommendations for the voluntary-insurance principle and other matters of method that are questions of an extremely controversial nature, and by the inclusion of which the framers detract from the force and value of their position.

Returning to the broad topic of social objectives, there is expectation that the President will include in a revised bill of rights, which it is thought he will present to Congress in the near future, as one among eight or so others, the right to adequate food, clothing, shelter and medical care.[4]

Thus we find evidence of growing acceptance of a new concept — Congress painting in the broadest terms the rights of man; the American Medical Association moving a considerable distance from its former reactionism to admit of similar objectives, but with reluctance to face the realities of their fulfillment; and the American Public Health Association directing its recommendations in a more or less intermediate path, recognizing the merit of the objective but at the same time aware of the difficulties besetting its accomplishment. These, of course, are not the only groups that have made recommendations based on prolonged study,[5–14] but in general these other proposals lie within the limits of the views of these two associations with respect to their objectives.

The plan must be practical and make provision for the logical steps by which it is to be developed. By and large, people who study and think about these things at all can be classed in one of four groups.

First, there are the *revolutionists*. I do not mean anarchists, but rather those who believe that mass social changes can be brought about by force of law. These are the persons who believe that the end justifies the means, and that where the processes of growth under our democratic system are slow, changes can be worked out in detail in advance in the minds of a few men and more or less set on the rest of their less informed fellowmen through the process of legislation and centralized administration.

Second, there are the *evolutionists*, the progressives, those who feel strongly the need of change or readjustment but admit the imperfections of the human mind in foreseeing the problems to be faced and in devising their solution other than by a process of trial and error. To this process they add a provision for a positive sort of force pushing things along. These persons like to think of progress as a step-by-step procedure at a reasonably accelerated rate.

Third, there is a group who might be called the *slow evolutionists*, a somewhat more timid folk, sometimes called conservatives. They are too rational and objective in their approach to deny the desirability of progress, yet they are too fearful, either because of their innate nature, because of misgivings or because of personal risks involved in change, to wish to encourage it openly.

Finally, there is a fourth group, who, at the risk of being hackneyed, I can only refer to as the "worry birds," which, as is well known, fly backward because they do not dare to face where they are going but always like to talk about where they have been. This group, in my opinion, is typified by those usually called the *reactionaries*, the ones who state that because we have made creditable progress no further advance is necessary.

No doubt you have already classified your friends

and acquaintances, possibly yourself, in one or the other of these categories. I should regard myself, — quite possibly fallaciously but in any event with much company — as being in the best group — that is, an evolutionist. I am distinctly dedicated to progress, but by the very nature of my experience I possess the utmost respect for the problems that beset the path of such progress.

Each of you will inevitably evaluate plans on the basis of the classification in which you really fall, but I urge that by whatever standards you judge a plan, you consider it in the light of whether it provides practical solutions to the over-all needs as you see them and whether you see in it the structure for logical development.

The plan must meet the needs of and be acceptable to those whom it most greatly affects. Again, let me remind you that we are discussing planning in terms of the likelihood of its accomplishing its objectives. The plan must therefore be acceptable, first, since lawmaking is involved, to those who are delegated the responsibility for making laws; second, since technical skills are involved, to those most intimately concerned with the provisions for such skills — namely, the medical profession, hospital administrators and ancillary technical workers; and finally, since public support is essential, to the recipients of the service, who are the public.

Broadly speaking, lawmaking falls into several categories of origin. Legislative acts may arise from political expediency in which the legislators either negotiate among themselves for political advantage, frequently of a somewhat subtle nature, or such legislation is conceived and executed through executive or legislative planning independent of actually crystallized public opinion, often as a result of the demands of pressure groups operating as well organized minorities and in self-interest. On the other hand, legislation may arise from the "grass roots," either spontaneously or as a result of leadership functioning within the structure of the truly democratic system and involving the long and arduous road of public education to a point of public recognition and action in behalf of its own best interests.

It is worth taking a few minutes to comment on the influence of pressure groups in the medical field, because this will throw some light on legislative processes and give further emphasis to the need that has been mentioned of a much more vigorous sense of public responsibility on the part of the medical profession. Two examples in my recent experience may serve as illustrations.

The first, although it represents an abortive attempt of a pressure group, is one of serious proportions and may eventually succeed. In the State of New York there are approximately 25,000 licensed doctors of medicine and 400 licensed osteopaths. Beyond this group there are approximately 2000 chiropractors, some of whom have been practicing for many years under what they choose to term "practice without benefit of law." In something like twenty-three out of the last thirty years, this group has brought pressure for legislation to license chiropractors, and from time to time they have succeeded in the passage of their bill in one or the other branch of the Legislature. This year, although again defeated, they came extremely close to succeeding.

The interesting fact is that here is a relatively small group that, by persistence and an extremely well organized lobby involving elaborate testimonials and highly organized support from a relatively small proportion of the population, threatens to achieve its objective. In my opinion and that of many others, the licensing of this group to diagnose and treat illnesses of all types, with insufficient training and through the use of methods that we consider to be essentially unscientific, would constitute a step backward rather than forward in the state's responsibility for protecting public service. What they cannot achieve on the basis of scientific justification, however, they may perfectly well achieve eventually through the process of attrition, in which they exhaust the patience of the Legislature and in which the large mass of the public is more or less apathetic.

In this connection, it is interesting to note that the State Chapter of the American Federation of Labor threw its weight behind this bill in what appears to be a misguided attempt to bring about improved services for the workers whom they represent. Their attitude was obviously based on what might be regarded as a failure of the medical profession to recognize the painful and disabling effects of minor back injuries sustained in industry. These often do not present signs and symptoms sufficient to permit acceptance under workingmen's compensation. Similarly, and not infrequently, I suppose, these patients may have been summarily dealt with at the hands of physicians who have been beset by the problem of malingering. It appears, however, that they have been more sympathetically received by the chiropractor and quite possibly given some relief through his manipulations.

Another example of the activity of pressure groups in the medical field, which was successful, relates to the Emergency Maternity and Infant Care Program, sponsored by the federal government through the United States Children's Bureau. As you may recall, in the early stages of this program considerable controversy arose over the attempts on the part of the Children's Bureau and certain of the states to set standards limiting the provisions of this program to the services of doctors of medicine. It was not long, however, before a small but highly organized lobby, supported primarily, I believe, by the American Osteopathic Association, succeeded in having the authority for such restriction stricken from the powers of the Children's Bureau. This they achieved through

introduction into legislation of phraseology to the effect that the wife of a serviceman must have the privilege of choosing the "practitioner of her choice," provided that state laws were complied with.

Although I do not wish to embark on the controversial subject of the relative merits of the training of osteopaths and doctors of medicine, the important point is that to obtain its objectives this particular group succeeded in defeating measures that were intended to protect the quality of medical care being provided to wives of servicemen. In so doing, they opened the door for inclusion under the provisions of this program of that large variety of practitioners and cultists who we all know are permitted to practice in some states.

With respect to the acceptability of a national medical-care program, there will be certain fundamental differences in the manner in which such a program impinges on the interests of the medical profession on the one hand and of the consumer public on the other. Obviously, the public will show its greatest concern over two questions — first, whether what it regards to be adequate medical services are physically available, and second, whether they are within economic reach. In general, unless medical facilities are totally lacking, it seems that the public is likely to address its primary consideration to the economic aspects — witness the current increase in the public support of voluntary hospitalization-insurance and medical-insurance schemes.

What the public accepts as good for it in terms of quality as well as quantity of care, however, will probably be determined more by a superficial comparison of the facilities in the community with those in other communities of a similar nature than by any expert evaluation of the services actually available. And in the field of preventive medicine, of course, other than in connection with traditional public-health measures, there is a great lack of public understanding.

I recall the surprise of a young lawyer in the Army returning home on leave who occupied the seat beside me on a plane not long ago. We fell to discussing the problem of medical care, and he seemed quite well informed. In common with most people, however, he believed that voluntary health insurance, supplemented by tax-supported care for the indigent, was pretty well on its way and that it left little to be desired. I was pleasantly surprised and encouraged by his change of attitude when I pointed out to him many of the facts that have already been covered in this series of lectures in relation to the inadequacy of facilities, the varying degrees of skill and opportunity to acquire and to maintain skill on the part of men in practice, the general absence of any systematic way of providing consultation services and specialist services other than in the large centers and the fact that the schemes that seemed to him to provide such a complete answer have fallen far short of doing so.

We cannot, however, hope to reach a large number of people with such a direct approach. We must be prepared to accept the fact that it probably will be easier to satisfy the public as it currently, and somewhat superficially, sees its needs than it will be to obtain public support of the type of program that will be in the best interests of the public well-being in the long run.

So far as the medical profession is concerned, acceptance of any sort will be difficult to predict. Consider, for example, the conclusions that we should have been obliged to draw if faced with this question ten years or so ago. We should have had to expect a complete lack of medical acceptance of hospitalization insurance or voluntary medical-indemnity insurance. Both these were formally resisted by the organized profession, but both of them are endorsed by it today. Similarly, at the time of its inception the Emergency Maternity and Infant Care Program was violently resisted by medical societies throughout the country, some of which held out until growing public opinion forced them to reverse their views. In spite of this, the program is now a going concern, widely and not infrequently enthusiastically accepted by physicians who are practicing under it. To be sure, important modifications have contributed to its acceptance, but it still is much different from the form that these groups in their first demands would have had it take.

These experiences lead to the conclusion that perhaps the medical profession is far more socially minded and far more willing to co-operate with logical and well planned steps of a progressive nature than those who have been leading the opposition to change and progress would care to have us suspect. I have proceeded over a period of years in the conviction that this is true, and I am happy to say that my experience has borne it out.

Certainly the average physician is far too intelligent to accept for long the almost childish manner in which the proponents of reactionism have dealt with him. It appears that all that has prevented the physician from penetrating such methods sooner has been the fact that he has been extremely busy and has usually given superficial, transient and often emotional acceptance to such leadership. But when faced with the real issue and the grave necessity of acting in the face of it, I am confident that he will vindicate himself.

I do not wish to be understood as taking the view that there are no grave problems involved and that the practicing physician should not be concerned, or that there is no danger of the introduction of unreasonable practices through the bureaucratic control of medicine. Judging from the patterns of past experience, there is undoubtedly reason for concern, but this danger will be far less, and probably need not materialize at all, if the medical profession will assume a vigorous and constructive role in

guiding the form of the impending changes that are of such importance to it.

There seems to be great fear of governmental control over the physician's salary check and of interference between him and his patient in the monetary contract area, as well as apprehension that a system of salaried positions would result in suppression of the physician's individuality and his opportunity to pursue his work with energy and freedom, and that he would be badly paid.

My own experience provides a case in point. I have been a salaried employee with the government of the State of New York for almost ten years. I am neither so rich as some of my classmates nor so poor as others. Not once during the ten years of my employment have I felt the slightest impact of a political nature. Although the question of freedom to work as one wishes is probably a matter that resides as much with the individual as with the system, I have found in the conditions of my employment even greater and less restricted opportunity to develop my interests and to expend my energies in directions that I consider to be worthwhile and productive than I encountered during the period of my private practice.

I have never been able to understand the insistence of fellow physicians on the importance of the privilege of negotiating a direct financial arrangement with their patients. I can recall vividly the extreme distaste with which, as a young man opening an office, I discussed the matter of compensation with my first patient. Somehow or other, it did not seem compatible with the whole philosophy that had stemmed from my training and experience up to that time, and I had a haunting feeling that I should pay the patient for the privilege of working on him those skills that, to me, were a matter of such interest and personal satisfaction.

From a somewhat less emotional and perhaps more practical point of view, it certainly seems that the medical profession would do well to look at the economic aspects of medical care from a strictly realistic angle. If we were to assume that the cost of medical care is comprised primarily of physicians' fees, which, of course, it is not, — and that the values in medical service are comparable to a manufactured product in the luxury class, — which they are not, — the medical profession would be justified in insisting on its right to name its price and to control the conditions under which this product is purchased.

But, obviously, we cannot regard any facet of the field of medical service in such a narrow light. The product of the physician is not a luxury; it is a necessity. In committing himself to a life of service in this field, the physician automatically assumes public responsibility, and in a sense, his life is no longer his own so long as he chooses to practice his profession. These things being so, if the economic aspects of medical service are such as to stand in the way of its complete accessibility to the public, I do not see how the physician can, in good faith, place his personal fears and considerations above changes that will serve the greater need. Even granting that he should do so, and that all of the more than 170,000 physicians in the country were unanimous in their point of view, I do not see how the medical profession could expect, should it come to a battle, that their small voice would carry much weight against the interests of 140,000,000 people.

On the other hand, the public is not competent to judge the extent of its technical needs or to evaluate the quality of service required or being provided. Just as truly as it has the power to control the economic issue, it is powerless to develop and control the quality and equitable distribution of the services it needs. At this point it must enter a partnership with the medical profession. By the force of this very fact, the medical profession faces a great responsibility and is assured an opportunity, if it wants it, to build into any program provisions for the highest standards for service and continued development. Medical acceptance should be given to nothing short of this.

The plan must contain the substance for authority, responsibility and orderly administration. This area in planning is almost sure to give rise to great controversy. It is the area in which the medical profession fears that there will be created a dominating bureaucratic or political control; it is the area of potential regimentation, the danger point in what is so frequently and yet ambiguously referred to as "state medicine." It is the zone of fear because the reasons for it and the potential manner of its conduct are so completely misunderstood.

The history of the process of growth from almost any angle, physical or sociologic, reveals the same fundamental patterns from the period of rudimentary beginnings through expansion, in which trial-and-error is the principal controlling force, to eventual development into a system or a series of complex relations that is likely to be cumbersome and confused because of its size and its overlapping and conflicting activities.

At such a stage, organization becomes essential to survival. This has been true of the growth of our cities, our schools, our banking system, our transportation, our industry, our employment. As these have evolved from simple beginnings into more complex structures, certain forms of organization have had to be introduced. This organization is a form of government.

Similar problems of growth have arisen in relation to the distribution of medical services, preventive medical and public-health services and hospital services. The point has been reached at which there is a pressing need for an over-all master plan for the Nation, for the states and for the major subdivisions of the states that will incorporate patterns for the co-ordination and conduct of these services

in their proper relation to each other and to the other operating forces in the social structure.

There is often confusion with respect to the functions of leadership versus those of authority and administration, but these are not synonymous terms. The medical profession outside of government may very well be so intimately and thoroughly concerned with the affairs of practice, teaching and research that it cannot be expected to develop either the skill, the time or the interest to assume responsibility with respect to authority and administration. Although the profession must recognize its limitations in this respect, it should also recognize the importance and the significance of the contribution that can be made by government — because this is the proper function of government.

It is a peculiar anachronism that while we stand staunchly behind our belief in the democratic system and are now fighting for it, many of us simultaneously deprecate and abuse it by our words and attitudes. Why has organized medicine acquired such a violent, almost reflex response to the word "government," as though assuming that government is inevitably evil? Evidently, it is all right for government to be concerned with matters related to other people, but not for it to set its hand in any way on the affairs of medicine.

Pursuing this line of reasoning, we are obliged to conclude that the medical profession must either believe that it is capable of meeting the needs of the future under circumstances that will permit it to act as its own administrative agent and endow itself with the necessary authority or that it does not recognize the need of administrative functions in the manner in which I have described them. I can only assure you that the task of steering the ship of progress through the trials and obstacles that will lie in its charted course are, in this case, not matters of minor consideration. They will require the exercise of rare judgment in trained hands.

The medical profession makes much of its right to lead, and I too believe this, but we can properly raise the question of where this leadership lies or what its value in respect to the problems ahead is. Are we to look for it from the American Medical Association, which has a long record of inaction and negativism with respect to progress in this field? Are we to look for it from groups such as the newly organized Association of American Physicians and Surgeons, which, as you may recall, is attempting to rally physicians under the banner of organized passive resistance to any government-sponsored medical-care program?

The positions of these groups certainly do not constitute auspicious bridgeheads from which to expect to advance in the areas to which we are addressing ourselves. I believe, however, that true leadership from within the medical profession can and will be found, and that in its over-all planning and in developing the mechanics of administration government should not be permitted, as an agent of the public interest, to proceed in the absence of such medical leadership.

Not so long ago I attended a meeting of a committee of a major national medical group at which problems arising from some of the existing federal programs in the field of medical care were under consideration. The purpose of this meeting was to establish patterns for so-called "co-ordinated action" between this national group and the controlling federal agency. There was a strong inclination on the part of the practicing physicians present to set up a special committee and to place before the federal agency what would have been little less than a demand that in the future this agency should call regular meetings of the special committee for the purpose of submitting its proposed policies for criticism and review. I am a strong advocate, as should already be clear, of medical co-operation with government and of the increasing influence of the medical profession in the control of medical affairs, but I opposed this suggestion. My opposition was conditioned by the belief that the proposed relation was essentially a negative one, based on the expectation of antagonism, and that although it might succeed in lessening some of the undesirable features of a potentially bureaucratic program, it would miss its real opportunity. In its place, I believed that it would have been better to have advocated a constant, co-operative working relation in which planning was mutually undertaken and in which the physicians were consulted during the formative stages of planning before conclusions had been reached and plans already drawn that would tend to make discussion become criticism and co-operative effort more or less futile.

It seems evident that no plan can succeed that does not embrace provisions for authoritative control and skillful administration. This I believe to be the function of good government. But equally I believe that good government must provide for the influences of effective guidance and leadership on the part of those who have the most to contribute. In the problem under discussion this would mean medical guidance and leadership.

The plan must be flexible with respect to local situations and future developments. This final principle is primarily a philosophy of planning, but it is also a test of the sincerity of purpose of the persons developing the plan. The plan at the national level, it seems to me, must be so fundamental and restrained in its approach to detail that flexibility will not constitute a problem. It is at the state and local levels, where working plans must be devised within the broad national pattern, that planned flexibility becomes a requisite.

Let me illustrate. A given state may start out with an attempt to set up a pattern of medical and health centers based on the health-center concept. Well and good. But supposing it en-

courages a group of hospitals to avail themselves of federal grants and postwar construction funds, only to find that it has gone ahead too rapidly and developed the centers in poor localities or in areas where they are not required. The state would then be confronted with a frozen front involving large investments of public funds and equally large and immovable investments in local public interest. The state program in such an instance would suffer from poor planning and inflexibility. On the other hand, if the plan had developed its physical system in the wake of rather than ahead of its services, or at least a reasonably accurate concept of the details of such services, it would have retained flexibility during a critical period. Moreover, the services, not the brickwork, would remain the focal point — obviously a situation more favorable to such changes as the future might necessitate.

I have somewhat the same concern with respect to the potential rigidity of voluntary hospital and other insurance plans. Good as they may now seem, they are not the answer to the total problem, and they may become obstacles rather than aids to further progress unless their limitations are clearly recognized by those sponsoring and controlling them. Although such insurance plans may help to meet the costs of medical care, they will do little to improve its quality or to bring about a better distribution of special skills and facilities. Also, they may divert public enthusiasm from the more fundamental issues because they are a sort of halfway measure in the right general direction. Once they are well under way, with large investments and a large following, they may well stand in the way of rather than assist further progress, unless open-mindedness and an unusual degree of social consciousness are written into the substance of their charters.

The need for flexibility will run through many other aspects of planning that embrace experimental or temporary expedients. For example, it will probably be necessary, strictly as a matter of acceptability, to employ a fee-for-service basis for compensating physicians at the outset. Yet experience has clearly demonstrated that this is not the best solution, and room should be left for further changes as opportunity may present and experience may justify.

As has already been stated, flexibility in planning is almost an abstract quality, a matter of vision and sincerity. Yet no plan will be realistic that lacks it.

* * *

In preparing the material for this discussion I had both a purpose and a hope in mind. My purpose was to try to give you a glimpse of the problems surrounding the field of medical care as seen through the eyes of a physician in government — in the specialty of medical administration, if you will permit me to call it such.

My hope was simple and not too visionary. I hoped, and still hope, that you — or at least some of you — will carry this discussion much farther in your own minds and that it may prove of assistance to you in the continued development of your interest in the medical needs of the Nation. And I hope that you will be ready to carry your share in assuring that whatever steps are taken shall be forward steps.

References

1. Goldmann, F. Foreign programs of medical care and their lessons. *New Eng. J. Med.* **234**:155-160, 1946.
2. Medical care in national health program. Official statement of the American Public Health Association, adopted October 4, 1944. *Am. J. Pub. Health* **34**:1252-1256, 1944.
3. Council on Medical Service and Public Relations. Regional conferences discuss medical problems. *J. A. M. A.* **127**:528, 1945.
4. *National Resources Planning Board: Report for 1943.* Document 128. Seventy-Eighth Congress. First session. Washington, D. C.: Government Printing Office.
5. *Interim Report from the Subcommittee on Wartime Health and Education to the Committee on Education and Labor, United States Senate.* Subcommittee Report No. 3 (January, 1945).
6. *Social Security Principles and Problems Arising out of the War.* Twenty-sixth session, International Labour Conference, Report IV, Part 1 (1944).
7. *Principles of Nation-Wide Health Program.* Report of Health Program Conference, Committee on Research in Medical Economics (November, 1944).
8. *National Health Program.* Report of Technical Committee on Medical Care, Interdepartmental Committee to Co-ordinate Health and Welfare Activities (1938).
9. Miscellany. Committee of physicians for presentation of certain principles and proposals in provision of medical care. *New Eng. J. Med.* **217**:798-800, 1937.
10. *Report of Committee on Consideration of Child Health in Postwar Period: American Academy of Pediatrics* (November, 1944).
11. *Medical Care for the American People.* Final report of Committee on Costs of Medical Care. 213 pp. Chicago: University of Chicago Press, 1932.
12. *National Resources Development Report for 1943.* Seventy-Eighth Congress. First session. Washington, D. C.: Government Printing Office.
13. Report of the Council on Dental Health, American Dental Association. *J. Am. Dent. A. Mid-monthly* **31**:1547-1566, 1944.
14. Statement of American Hospital Association in regard to hospital care. *Hospitals* **18**:November, 1944.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 32091

PRESENTATION OF CASE

An eighteen-year-old boy was admitted to the hospital complaining of pain in the left arm.

Four months before admission, while roller skating, he fell, experiencing a sensation of something snapping in the left back under the scapula, this being accompanied by pain. On arising, he was unable to use the left arm because of pain in the shoulder. This pain was aggravated by coughing and radiated to the anterior chest. During the next two weeks, the shoulder pain subsided and he recovered full use of the arm; the chest pain, however, was still present when he coughed. Three weeks before admission he first noticed prominent veins in the upper portion of the left arm. At the same time a constant dull ache appeared along the posterior portion of the left upper arm and became progressively severer. Ten days before admission he was examined by his draft board and advised to go to a hospital immediately.

Two and a half years before admission the patient had migratory joint pains, as well as a red rash on the anterior aspect of both legs. A cardiac murmur was heard at that time but later disappeared. He had had scarlet fever at the age of four years.

Physical examination revealed a well developed and well nourished boy in no acute discomfort. The pupils were regular and equal and reacted to light and accommodation. The thyroid gland was not palpable. The trachea was in the midline. In the left anterior triangle of the neck was a firm mass about 2 cm. in diameter, which was continuous with a larger mass in the left supraclavicular fossa near the midline; the larger mass was firm, nontender and irregular. A systolic bruit was heard over an area including the larger mass and the left clavicle. There was dullness to percussion over the apex of the left lung, more marked posteriorly. The breath sounds were absent in this area, with decreased tactile fremitus; otherwise the lungs were clear. The heart was negative. Discrete hard nodes about 5 mm. in diameter were palpated in the left axillary region. The abdomen was negative. The left hand was cold and blue. The biceps and triceps reflexes could not be elicited on either side.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure on the right was 120 systolic, 80 diastolic, and on the left, 116 systolic, 90 diastolic.

The red-cell count was 4,700,000, with 15 gm. of hemoglobin. The white-cell count was 11,100, with 67 per cent neutrophils. The urine and stools were normal. An x-ray film of the chest revealed a soft-tissue mass measuring 8 by 6 cm. in the left upper chest. It was slightly lobulated and continuous with the lateral chest. The remainder of the lung fields was clear. The heart, aorta and diaphragmatic shadows were not remarkable. The first rib on the left was not clearly visualized in its anterior two thirds, but there was a fracture at the junction of the middle and posterior thirds; the second rib on that side was not remarkable. Pulsation of the mass was not noted fluoroscopically.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CLIFFORD C. FRANSEEN: May we see the x-ray films?

DR. MILFORD D. SCHULZ: A soft-tissue mass lies in the apex of the left chest laterally and anteriorly. The anterior and lateral portion of the first rib is destroyed (Fig. 1).

DR. FRANSEEN: Where is the fracture?

DR. SCHULZ: I cannot see the fracture. The mass appears to be outside the lung.

DR. FRANSEEN: The age of the patient is of primary importance in any bone tumor. I shall discuss this point later. Another important bit of evidence is the fact that he fell and had a snapping pain in the left scapular region. That pain could have been due to a pathologic fracture of the first rib. If there was a fracture, as was interpreted, the pain later eased up some but was still present when he coughed. The next episode was three weeks before admission when he first noticed prominent veins in the upper portion of the left arm, with an ache posteriorly. All this was undoubtedly due to the position and size of the tumor, pressure on the subclavian vein causing the prominent veins. The earlier findings of migratory joint pains and a cardiac murmur apparently have no relation with the present problem.

So far as the physical examination goes, the important thing is the 2-cm. mass that was continuous with a larger mass in the left supraclavicular fossa. The fact that it was continuous is perhaps important because we are interested in knowing whether this was a tumor that had metastasized or a primary tumor that had extended in this region; this one point alone may be significant in the differential diagnosis. A systolic bruit was heard over the mass, which can be accounted for on the basis of pressure on the vessels, particularly on the subclavian artery.

Nodes 5 mm. in diameter were found in the left axillary region; one cannot put much importance on nodes of this size in the axilla. The arm reflexes could not be elicited, undoubtedly because of pressure on the brachial plexus.

This seems clearly to have been a tumor. What organ did it originate in? We can exclude the lung by the x-ray interpretation. Could it have arisen in the pleura? The tumors that might come from the pleura in this region are the endotheliomas and the sarcomas. They are frequently associated with effusion, which was not present here. Was this something outside the bone invading it secondarily or was it primary in the bone? Could it have originated in the lymph nodes and then have invaded the bone? The first thing to think of at this age is Hodgkin's disease. We know that such a tumor frequently invades bone, but to me this is not the picture of Hodgkin's disease. Hodgkin's involvement of bone usually comes after the disease has been progressive for a year or two, and then not by direct extension, as this must have been. Still other extraosseous tumors that could have invaded the bone are the lymphangiomas and the hemangiomas, but they do not seem likely. There is nothing to suggest a tumor of neurogenic origin. The neurologic signs here can be interpreted on the basis of pressure. One cannot entirely exclude fibrosarcoma, except to some extent on the appearance of the x-ray films; it is conceivable but unlikely.

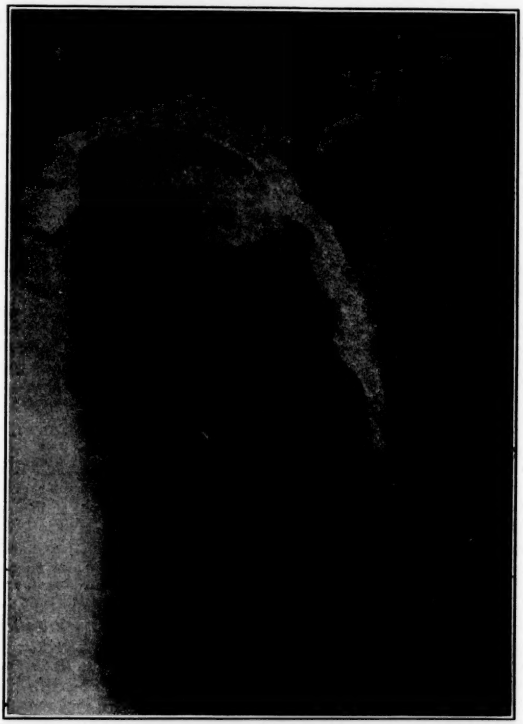

FIGURE 1.

If we consider this to be a lesion originating in the bone we must ask, as Dr. Channing Simmons has taught us, Was it infectious? Was it metabolic? Was it neoplastic?

There is not much about the appearance of the mass or the systemic reaction to suggest that it was infectious — pyogenic, tuberculous or syphilitic. No serologic test is reported, but it is safe to say

that it was done, because it is almost an invariable rule in any case of bone tumor to rule out syphilis, which can simulate most of these lesions. Another condition that comes to my mind, because I was caught on it three years ago, is an eosinophilic granuloma of the rib. That condition, however, shows a somewhat punched-out area in the rib, and I know of no case in which a tumor mass has been produced. Thus, there is nothing in this case to suggest an infection; nor is there anything to suggest a metabolic disturbance.

So we come to the fact that it must have been neoplastic. Was it benign or malignant? The regular contour suggests a benign lesion. Was it metastatic or primary? The metastatic lesions that occur at this age are few. Ewing's tumor can metastasize to a rib; the other metastatic lesions that occur in children, such as the neuroblastomas, usually appear at an earlier age, and there is no clinical or other evidence to suggest that metastases had occurred.

This then appears to have been a primary tumor, and the differential diagnosis lies between myeloma, Ewing's tumor and osteogenic sarcoma. We can discard myeloma because the great majority of them occur in patients over forty and the tumors are usually multiple. The only thing that suggests it is the pathologic fracture, because statistically 50 per cent of cases of myeloma have pathologic fractures at some time during their course, frequently in the rib. In this case I believe that we can exclude it on the basis of age alone.

How about Ewing's tumor? Ewing's tumor originates in the spongiosa of the bone and is not a cortical destructive lesion; therefore not many pathologic fractures occur with it. Another possible reason for the absence of fractures in Ewing's tumor is that pain is so prominent that the bone is protected, particularly the long bones.

When osteogenic sarcoma does occur in the rib, it is usually the sclerosing type, but the chondroblastic type is likelier to have pathologic fractures because of the bone-destructive effect.

So I have narrowed the diagnosis down to osteogenic sarcoma, with its variations, and Ewing's tumor. This patient was eighteen years old, an age group in which both these tumors occur; in Ewing's tumor 95 per cent of the patients are below twenty-five years of age. This site is rare in both tumors, although both do occur there. I have never seen a Ewing's tumor of the rib in this country, but I did see three in quick succession in Sweden — all rare diseases seem to come in groups of three.

The other thing to be considered in the differential diagnosis of this case is the presence or absence of metastases. Was the tumor mass in the anterior triangle of the neck a metastasis or was it continuous with the primary tumor? This is quite a long way for a tumor of the rib to extend, but it would be likelier in a case of Ewing's tumor than in one of osteogenic sarcoma. Metastases in osteogenic sarcoma are extremely rare. I have only seen two such cases — one a paravertebral metastasis, and the other a case in which there were bone-forming metastases in the axilla. It does occur, however, as I have said, more commonly in Ewing's tumor than in osteogenic sarcoma. Ewing's tumor, as you know, is usually accompanied by a febrile reaction. This patient was in good general condition on physical examination. On a statistical basis, two thirds of all malignant tumors of bone are osteogenic sarcoma. If this was osteogenic sarcoma, what is the likelihood of the sclerosing form? Osteogenic sarcoma in the rib is usually sclerosing, but there is not much about the x-ray picture to suggest that this was a sclerosing type of tumor. The other form is chondrosarcoma or chondromyxosarcoma. From the evidence we have, I favor a primary tumor of the costal cartilage of the right first rib — a chondrosarcoma, possibly with myxomatous elements. As you know, such tumors invade along the rib, which makes it necessary to remove the entire rib. In any case, one should not be satisfied in removing the tumor alone; if possible, the entire rib should be removed.

DR. BENJAMIN CASTLEMAN: Dr. Richardson, have you any comment?

DR. WYMAN RICHARDSON: This patient was on the medical service for a short time and I made a diagnosis of malignant tumor and yelled for Dr. Simmons.

DR. CASTLEMAN: Dr. Berg, you also saw this patient.

DR. ROBERT L. BERG: Dr. Helen Pittman saw him on the first day and thought that a block resection should be done immediately because of the possibility of rapid extension. I think that we were all agreed on the diagnosis of malignant tumor, but like Dr. Richardson, no one tried to be more specific.

DR. RICHARD H. SWEET: My point of view was much like that of Drs. Franseen, Richardson, Pittman and Berg. It was obviously a malignant tumor. I made a preoperative diagnosis of chondrosarcoma, which is, in my experience, by far the most frequent primary malignant tumor of rib, as Dr. Franseen has said, excluding multiple myeloma. Although he has not seen any cases of Ewing's tumor of rib in this country, I saw one case some years ago; but I still regard it as a rather unusual occurrence. These were the two tumors considered in differential diagnosis.

From the clinical aspect of the case it was obvious that we were dealing with a malignant tumor and that the prognosis was bad. But it seemed to me that, with a young boy of eighteen in a remarkably good state of health, we should make an attempt to remove the tumor. It so happened that the first-year anatomy class was watching the operation from overhead, and it turned out to be a remarkable lesson in anatomy. In these days of

superspecialization, if I were called on to choose a surgeon to operate in such a case, I should not know whom to call, because the tumor involved the chest, the neck and all sorts of organs that are unfamiliar to most of us in the ordinary routine run of surgical practice.

I made an incision over the clavicle and resected the medial two thirds of that bone. That exposed the subclavian vessels, which were flattened and compressed to such an extent that it was difficult to see how any blood could get through either the vein or the artery. The tumor arose in the first rib and seemed to involve the second rib, although we thought that perhaps the second rib was merely pressed on by the tumor. For a long time I was uncertain whether to remove it, but ultimately got so far that I had to take it out. This involved tying the thoracic duct and removing long segments of the subclavian and axillary arteries, including the main collateral vessels and one or two others. In so doing, I thought that we would produce a permanent disability to the patient's arm; but since we were dealing with a malignant tumor, this had to be done. We forcibly retracted the brachial plexus. On opening the chest I discovered that the tumor had invaded a portion of the upper lobe of the left lung, and this part of the lung was removed. When we got down to the point where I thought that I had dissected away most of the tumor, I observed what appeared to be invasion of the scalene muscles beyond where I could trace it. So I took out a tremendous mass of tissue, including a tumor twice the size of what it appeared to be by x-ray, along with the piece of lung and the large sections of artery and vein. We could look into the patient's chest and see the heart and diaphragm from above. In order to improve the collateral circulation to the arm, I did a sympathectomy, removing the second and third dorsal ganglions.

The amazing thing is that following operation the patient had no trouble with the arm; although it was slightly weak, he used it well.

Clinical Diagnosis

Chondrosarcoma of rib.

Dr. Franseen's Diagnosis

Chondrosarcoma of rib.

Anatomical Diagnosis

Ewing's sarcoma of first rib, with extension into mediastinum, lung and neck.

Pathological Discussion

Dr. Castleman: The gross appearance was that of a meaty tumor, not the gelatinous type that one sees in a chondrosarcoma. There was tumor at the resected edge where Dr. Sweet had cut across, and histologic examination showed a rapidly growing Ewing's tumor. Following operation the patient received x-ray treatment with the million-volt machine. He may do well for a while, although I do not know of any cures of Ewing's tumor except one that Dr. Schulz told me about yesterday.

Dr. Schulz: In 1939, at the Huntington Hospital, a boy, then five years old, was seen in whom we discovered, more or less by accident, a tumor involving the right eighth rib. The lesion was biopsied, and sections were sent to quite a number of pathologists, who made the diagnosis of Ewing's tumor. X-ray treatment with the Huntington Hospital's million-volt machine was given, and he has been well since. This is one of the rare cases of Ewing's tumor in which the victim has survived for more than five years.

Dr. Castleman: The tumor was not removed?

Dr. Schulz: No.

Dr. Franseen: It would be interesting to know whether the mass in the anterior triangle was a mediastinal node that had become continuous or was part of the main tumor.

Dr. Castleman: No lymph nodes were involved. The tumor in the neck was an extension of the primary lesion.

CASE 32092

Presentation of Case

A fifteen-year-old girl was admitted to the hospital complaining of swelling of the face and legs.

One year before admission, following an upper respiratory infection, edema of the face, hands and ankles appeared, associated with dyspnea and orthopnea. There was no oliguria or hematuria. At another hospital the blood pressure was found to be 145 systolic, 100 diastolic. An intravenous pyelogram revealed normal calyxes, pelvis and ureter on the left; there was no function on the right. A retrograde pyelogram revealed a small contracted right kidney, with normal calyxes, pelvis and ureter. No calculi were found. While the patient was in the hospital, the blood pressure varied from 140 systolic, 90 diastolic, to 170 systolic, 40 diastolic. The nonprotein nitrogen varied from 36 to 49 mg. per 100 cc., and the serum protein from 3.6 to 4.3 gm. Albuminuria was constantly present. At the time of discharge, she was free of edema and felt well. She remained well until two weeks before admission, when, with the development of an upper respiratory infection, the same symptoms reappeared, accompanied by pain in the abdomen and in the costovertebral angles. There were no urinary symptoms. She felt fatigued, and a cough with tenacious sputum developed.

The past history was noncontributory. She had not had scarlet fever.

Physical examination revealed a well developed

and well nourished girl who was dyspneic and orthopneic and had a hacking cough productive of yellow, mucoid sputum. She was not cyanotic or jaundiced. The skin was pale. The eyelids and face were edematous. The tongue was dry and coated. A few small cervical lymph nodes were palpable. The heart was questionably enlarged to the left. There were no thrills or murmurs. Dullness to percussion, diminished breath sounds and moist rales were found over the right base posteriorly. The abdomen was diffusely tender, so that palpation was unsatisfactory. The liver edge was tender and palpable three finger-breadths below the right costal margin. Tenderness was also elicited over both costovertebral angles. The sacrum and lower extremities were markedly edematous.

The temperature was 98.6°F., the pulse 70, and the respirations 20. The blood pressure was 145 systolic, 114 diastolic.

The red-cell count was 3,500,000, with 10.2 gm. of hemoglobin. The white-cell count was 10,700, with 74 per cent neutrophils. The urine was cloudy and yellow, with a specific gravity of 1.008. It gave a ++++ test for albumin, and the sediment contained 50 to 60 white cells per high-power field; there were no red cells or casts. The Sulkowitch test for urinary calcium was negative. The nonprotein nitrogen was 125 mg. per 100 cc. The serum protein was 5.3 gm. per 100 cc., with 3.1 gm. of albumin and 2.2 gm. of globulin. The serum cholesterol was 164 mg. per 100 cc., the sodium 138.8 milliequiv. and the chloride 99 millequiv. per liter, and the calcium 7.6 mg. and the phosphorus 6.5 mg. per 100 cc. The prothrombin time was 27 seconds (normal, 18 seconds). A cephalin-flocculation test was negative in twenty-four and forty-eight hours. The van den Bergh reaction was normal. A blood Hinton test was negative. A throat culture was negative for beta-hemolytic streptococci. A sputum culture showed rare beta-hemolytic streptococci and a moderate number of Type 22 pneumococci. The urine was sterile.

A chest plate showed a considerable amount of pleural effusion bilaterally. The hilar shadows were quite prominent, but the lung fields were obscured in their lower half by the fluid. The heart shadow was not clearly outlined because of the adjoining density in the chest.

The patient was digitalized. She vomited occasionally. An electrocardiogram taken on the fifth hospital day showed sinus arrhythmia, with a rate of 100. QRS_1 was upright and low, T_1 flat, and QRS_2 slurred. The PR interval was 0.18 second. T_2 was low upright, QRS_3 slurred, T_3 slightly inverted, S prominent in CF_3, T flat in CF_3, and T low and upright in CF_4 and CF_5. Two days later a concentration test of renal function showed fixation of specific gravity at 1.006. A phenolsulfonephthalein test showed less than 10 per cent total excretion in two hours. The serum carbon dioxide content was 15.8 millequiv. per liter, and at that time the nonprotein nitrogen was 50 mg. per 100 cc. An intravenous pyelogram taken on the tenth hospital day showed extremely poor detail because of the large amount of fluid in the abdominal cavity. There was a small amount of gas in several loops of small intestine, without distention. The kidney shadows were not clearly outlined. Over a period of sixty minutes no dye was excreted by either kidney. The urinary passages were not outlined. Fair diuresis was obtained with Mercupurin, but nausea and vomiting persisted, the latter becoming projectile in nature.

On the nineteenth day the nonprotein nitrogen rose to 160 mg. per 100 cc. The patient became unresponsive. A gallop cardiac rhythm appeared. She expired on the twenty-ninth hospital day.

Differential Diagnosis

Dr. Arthur J. Linenthal: This patient had renal disease, as manifested in the clinical picture of the illness one year before admission and in the final episode, which was terminated by a combination of renal and cardiac failure. The problem is to determine the nature of the renal lesion.

The nephrotic picture of the disease, as evidenced by marked generalized edema, suggests glomerulonephritis rather than pyelonephritis or nephrosclerosis. In addition, the youth of the patient is against a primary vascular disease, and at no time was there evidence of urinary-tract infection. The edema and marked albuminuria raise the possibility of a degenerative disease of the tubules, that is, nephrosis, but the elevated blood pressure, evidence of renal failure and normal serum cholesterol are against this diagnosis. The pyelographic demonstration of a small contracted nonfunctioning right kidney is of interest, but the absence of obstruction or infection and the normal calyxes, pelvis and ureter suggest that this kidney was congenitally hypoplastic and that this anomaly was unrelated to the renal disease, although the kidney was probably involved in the inflammatory process, which is typically bilateral.

In attempting to explain this patient's illness on the basis of glomerulonephritis, the question arises whether the episode one year before the final admission represented an acute process or an exacerbation of a chronic stage of this disease. The absence of hematuria is somewhat puzzling in either case. The relation to an upper respiratory infection and the edema, dyspnea, orthopnea, elevated blood pressure, albuminuria and slightly elevated nonprotein nitrogen are of little differential value. Aside from the rather low serum protein, which suggests a chronic process, there is nothing further to aid in the differentiation.

We are not told the duration of this first period of illness, but the patient recovered completely so far as symptoms are concerned and was well until shortly

before the final admission. It would be interesting to know whether albuminuria or hypertension persisted throughout the long asymptomatic interval. Two weeks before admission she again became ill, went downhill quickly in the hospital, and died six weeks after the return of symptoms.

The terminal uremia was typical of that seen in chronic glomerulonephritis, as well as in other types of chronic Bright's disease. Severe renal failure was shown by the low fixed specific gravity of the urine, the greatly diminished or absent excretion of dye in the renal-function test and following intravenous pyelography respectively, the markedly elevated nonprotein nitrogen, the lowered serum calcium, the elevated phosphorus and the lowered carbon dioxide content. The serum sodium and chloride values were within normal limits. The moderate anemia is a frequent finding in uremia.

Like the earlier episode, the onset of this illness, apparently an acute exacerbation of a chronic glomerulonephritis, accompanied an upper respiratory infection. She had a cough and raised some sputum, which showed Type 22 pneumococci on culture. The pleural fluid obscured both the physical and x-ray examinations and made it difficult to be certain whether or not these organisms were associated with a pneumonic process. The normal temperature and the only slightly elevated white-cell count suggest that no significant pulmonary infection was present.

Again, edema of the eyelids and face was a striking feature of the clinical picture, and the serum protein was somewhat low. Part of the generalized edema was due to cardiac failure, which will be considered later, but much of it was of the nephrotic type, a common feature of chronic glomerulonephritis. The patient had pain in the abdomen and costovertebral angles, which is often seen with an exacerbation of a chronic process of this sort.

The urinary findings are of interest. Albumin and white cells were found, although, despite the severe degree of renal damage that was present, no red cells or casts were seen. Presumably the marked pathologic changes in the kidneys in this terminal stage prevented the excretion of these elements.

Congestive heart failure, so often seen in chronic glomerulonephritis, was manifested in this patient by dyspnea, orthopnea, dependent edema, bilateral pleural effusions, enlarged hilar shadows, ascites, a gallop rhythm and an enlarged tender liver. The heart size could not be definitely determined by physical or by x-ray examination. Liver function, as tested by the cephalin-flocculation test, the prothrombin time and the van den Bergh reaction, was normal. Digitalis and Mercupurin gave some diuresis, but death occurred due to a combination of uremia and cardiac failure.

Clinical Diagnoses

Chronic glomerulonephritis.
Uremia.
Cardiac failure.

Dr. Linenthal's Diagnoses

Chronic glomerulonephritis, with uremia.
Congestive heart failure.
Congenital hypoplasia of right kidney.

Anatomical Diagnoses

Chronic glomerulonephritis of left kidney.
Congenital hypoplasia of right kidney.
Congenital malformation of left kidney.
Cardiac hypertrophy, hypertensive type.
Pericarditis, uremic.
Anasarca.
Bronchopneumonia.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Linenthal has accurately predicted the pathological findings in the kidney. The right kidney was extremely small, weighing only 10 gm. The pelvis was quite normally developed, but the renal parenchyma consisted only of a shell 2 mm. in width in which no structural detail, such as differentiation into cortex and medulla, could be observed. Microscopically the sections showed only a single glomerulus and a mass of undifferentiated tubules filled with dense colloid casts. Except for a slight pyelitis there was no evidence of inflammation, and the picture is that of a congenitally hypoplastic kidney. The left kidney was also markedly abnormal in development, consisting of two almost separated lobes. It weighed 95 gm. The capsule stripped with difficulty and left a finely granular surface. Microscopical examination revealed great destruction of the glomeruli, widespread interstitial fibrosis and marked dilatation of the persisting tubules. The blood vessels showed extensive secondary sclerotic changes. There was no evidence of acute progressive glomerulitis. The chronicity of the process answers Dr. Linenthal's question about the first admission. It seems quite certain that she must have already had a chronic process at that time.

The other findings at autopsy were such as might be expected in a case of chronic nephritis. There was a terminal fibrinous pericarditis, and the heart was slightly hypertrophied. The lungs showed edema and focal pneumonia. There was generalized edema.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board
Joseph Garland, M.D. A. Warren Stearns, M.D.
Shields Warren, M.D. Chester S. Keefer, M.D.
C. Guy Lane, M.D. Fletcher H. Colby, M.D.
William A. Rogers, M.D. Robert L. Goodale, M.D.
Henry R. Viets, M.D. Chester M. Jones, M.D.
Robert M. Green, M.D. Harvey R. Morrison, M.D.
Charles C. Lund, M.D. Maxwell Finland, M.D.

Associate Editors
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.
Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year (Boston funds); $8.52 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

EARLY DIAGNOSIS AND TREATMENT OF DIABETIC COMA

During the seventy years that have elapsed since the discovery of the ferric chloride test for diacetic acid in the urine, intensive study of ketosis as it occurs both in diabetes and in nondiabetic states has greatly increased knowledge concerning its relation to the metabolism of carbohydrate, protein and fat.

In diabetic coma the essential disturbance in carbohydrate metabolism is due to the relative or absolute lack of insulin. Ketosis and ketonuria follow the failure to utilize sufficient carbohydrate and the consequent increased formation of ketone bodies from fat. The discovery of ketonuria in a diabetic patient should always be taken as an emergency sign indicating the need for further study of the patient and prompt treatment. Although tests for acetone and diacetic acid may be strongly positive in the urine of some patients who have not as yet developed severe acidosis, ketosis is eventually accompanied by dehydration and loss of base. Numerous methods for ascertaining the degree of acidosis have been employed, such as determinations of the total acetone bodies in the blood, of the hydrogen ion concentration of the blood and of the excretion of ammonia in the urine. The degree of acidosis may also be determined accurately by measurements of the carbon dioxide content of the blood. If the carbon dioxide content of the blood has fallen from the normal of 26 millimols per liter (60 volumes per cent) to the neighborhood of 13 millimols (30 volumes per cent), a moderate degree of acidosis is present. When it has fallen below 9 millimols, experience indicates that, if unconsciousness has not already developed, its onset is a matter of hours and that the terminal stage of shock and anuria is impending.

In a recent article by Almy, Swift and Tolstoi* the value of determinations of the blood-sugar and of the blood-carbon dioxide levels in the treatment of diabetic coma is minimized. In their series, however, since only 19 out of 99 patients had the typical Kussmaul breathing of acidosis, it is evident that the series included a large number of extremely mild cases of ketosis, although chemical data are not given. Indeed, only 1 patient was unconscious, and several of 7 who died had complicated cases. A more general teaching is that diabetic acidosis and coma are emergency states in which a careful study of the patient and chemical determinations of the sugar level and for evidence of acidosis in blood and urine are essential to the best type of treatment. A diagnostic pitfall to be avoided lies in the fact that, although ketonuria at first may be excessive, in the more advanced stages with renal failure, ketone bodies are no longer excreted in the urine. More emphasis should be laid on early diagnosis of impending diabetic coma, since treatment with insulin at that time averts the later and more critical stages. As pointed out by Dr. Haigh in a letter published

*Almy, T. P., Swift, K., and Tolstoi, E. Treatment of diabetic acidosis and diabetic coma. *J. A. M. A.* **129**:863-868, 1945.

elsewhere in this issue of the *Journal*, aggressive attempts should be made to publicize these facts among physicians, as well as among diabetic patients.

More reports of the results of treatment in series of coma cases are needed to emphasize the serious prognosis in diabetic coma, especially in patients with unconsciousness and with complications. Laboratory facilities should be more generally available to all doctors for emergency determinations of the blood constituents, as aids both in diagnosis and in treatment. Prompt diagnosis and aggressive treatment in the early stages have been shown not only to relieve the acidosis but also greatly to enhance the patient's chance of recovery from an otherwise severe or fatal complication.

THE COMMITTEE ON GROWTH

In the past, the control and treatment of cancer has been attacked by many able men the world over, and it is unnecessary to point out that many notable advances have been made. It is true, however, that the problem of malignant neoplastic disease, which in essence is that of ceaseless, profitless and often uncontrollable growth, has been approached by individual groups of men with rather specialized training and abilities. There have been the pathologists, like the late Drs. Mallory and Ewing, who defined and delineated groups of cancer; there have been the clinicians, who have studied the natural history of the disease and have worked out helpful and even curative surgical measures; there have been the radiologists and physicists, who have greatly advanced the technical weapons with which cancer may be attacked; there have been the geneticists, the biologists and the chemists, who have enriched knowledge of hereditary factors and carcinogenic agents; and there have been the public-health officials, who, through appropriate and legitimate propaganda, have educated the public to seek medical advice earlier and to accept more readily the available hospital facilities. But, when all is said and done, it must be admitted that, as a general thing, these men, however able, worked in comparative isolation, each pursuing the line of investigation to which he was most suited and for which he was best trained. This is not to say that their contributions were not of the first order — they were: the tactics were excellent, but the overall strategy was perhaps lacking or at best in the background.

As has been said, the essence of the problem is that of ceaseless, profitless and often uncontrollable growth. It is therefore gratifying that there has been created within the Division of Medical Sciences, National Research Council, the Committee on Growth, which as a body will function as a scientific adviser to the American Cancer Society. This committee is a true board of strategy, an integrating body composed of the foremost men in their respective fields. By their general direction and with their combined and unified help it may properly be hoped that the solution of the cancer problem is nearer at hand. Under a general staff headed by Dr. Cornelius P. Rhoads and including such outstanding scholars as Drs. Dochez, Hastings, Sabin, Little and Winternitz, there are divisions of biology, chemistry, clinical investigation and physics. Within these divisions are panels covering such diverse departments as radiology, endocrinology, nutrition, enzymes, mutation and botany. Each of these panels, in turn, is headed and staffed by outstanding investigators, such as Drs. Cowdry, Dubos, Albright and Castle. Presumably it is the intent of this excellent committee to integrate the existing investigations in the field of cancer and to initiate new ones. If such be the case, — and there is every reason to believe that it is, — the future of cancer investigation is bright indeed.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Lowell	March 1	Albert H. Brewster
Salem	March 4	Paul W. Hugenberger
Haverhill	March 6	William T. Green
Brockton	March 14	George W. Van Gorder
Worcester	March 15	John W. O'Meara
Pittsfield	March 18	Frank A. Slowick
Springfield	March 19	Garry deN. Hough, Jr.
Fall River	March 25	David S. Grice
Hyannis	March 26	Paul L. Norton

Physicians referring new patients to clinics should get in touch with their district health officers to make appointments.

CORRESPONDENCE

DIAGNOSIS OF DIABETIC COMA

To the Editor: It is regrettable that, even though a specific remedy has been available for nearly a score of years, patients still die of diabetic coma. Since the subject is no longer beclouded by theories, not only unsound but useless, such deaths are inexcusable.

Too few of my interns and residents have grasped the simplest concept of diabetic coma: it is a fatal sign of immediate danger from what is essentially a deficiency disease, an insufficiency of insulin not merely in the blood but in every cell in the body. Hence the primary factor in treatment is the degree of acidosis, whereas hyperglycemia and dehydration are but secondary, even incidental. Accordingly, instead of repeated blood-sugar examinations, tests for ketosis are obviously more reliable guides to the amount of insulin needed promptly and directly to restore the deficiency and thereby save the diabetic patient. Simple tests for urinary acetone and diacetic acid are usually preferable to determinations of the blood-sugar level.

G. W. Haigh

242 Burncoat Street
Worcester 6, Massachusetts

NOTICES

ANNOUNCEMENTS

Dr. Joseph S. Barr, having returned from service with the United States Navy, has resumed practice at 234 Marlborough Street, Boston.

Dr. Weston T. Buddington, having returned from military service, announces the opening of his office for the practice of urology at 12 Bay State Road, Boston.

Dr. S. Forrest Martin announces the opening of his office at 101 Bay State Road, Boston, for the practice of ophthalmology.

Dr. Channing S. Swan announces his return to the private practice of urology with offices at 20 Gloucester Street, Boston 15.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, March 12, at 8:15 p.m. Dr. Nathan Rosenthal, of the Mt. Sinai Hospital, New York City, will speak on the subject "Blood Cell Reactions to Drugs." The paper will be discussed by Drs. William Dameshek, Maxwell Finland, and Benjamin Alexander.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, March 7, at 7:15 p.m. in the classroom of the Nurses' Residence. Dr. Eliza A. Melkon will speak on the subject "Allergic Manifestations after the Injection of Varicose Veins," which will be followed by a discussion by Dr. Eda A. Polcari. Dr. Dorothy K. Scheidell will be chairman.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston

Lecture Hall, 9-10 a.m.

Medical Conference Program

Friday, March 1 — Treatment of Psychiatric Problems: Case discussion. Dr. Mandel E. Cohen.
Wednesday, March 6 — Carcinoma of the Uterus. Dr. Louis E. Phaneuf.
Friday, March 8 — Streptomycin. Dr. Donald Anderson.
Wednesday, March 13 — To be announced. Dr. Harold A. Abramson.
Friday, March 15 — Clinicopathological Conference. Drs. Chester S. Keefer and H. E. MacMahon.
Wednesday, March 20 — Diagnostic Errors in the Pratt Hospital. Dr. C. B. Popplestone.
Friday, March 22 — First Stages of Human Conception. Dr. John Rock.
Wednesday, March 27 — Roentgenological Changes in Sprue and Other Nutritional Disturbances. Dr. Alice Ettinger.
Friday, March 29 — Some Aspects of Military Orthopedics Applicable to Civilian Practice. Dr. Joseph S. Barr.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted by some of our staff members from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

The first postwar annual meeting of the American Association for the Study of Goiter will be held at the Drake Hotel, Chicago, on June 20, 21 and 22 — dates that are convenient for the majority of those planning to attend the meeting of the American Medical Association in San Francisco during the first week of July. Those who intend to be present at the Chicago meeting are advised to make their hotel reservations as early as possible.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, March 7

Friday, March 8
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
Monday, March 11
*12:00 m.–1:00 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.
Tuesday, March 12
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
Wednesday, March 13
*10:30–11:30 a.m. Medical Clinic. Isolation Building Amphitheater. Children's Hospital.
*12:00 m. Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Cambridge Hospital.
*2:30–4:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.
*7:15 p.m. Graduate Seminar in Pediatrics. Children's Medical Service, Amphitheater 3A, Massachusetts General Hospital.

*Open to the medical profession.

January 7–April 22, 1946. Metropolitan State Hospital. Eleventh Postgraduate Seminar in Neurology and Psychiatry. Page 314, issue of September 6.

February 4–March 29. Health Education Institute. Page 746, issue of December 13.

March 1–March 29. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Notice above.

March 7. New England Hospital for Women and Children. Notice above.

March 11. Massachusetts Hospital Association. Page 240, issue of February 14.

March 12. Greater Boston Medical Society. Notice above.

March 14. Bursitis at the Shoulder Joint: Diagnosis and treatment. Drs. Francis C. Hall and Robert B. Osgood. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

March 15–September 15. Boston University Course for Discharged Medical Officers. Page 240, issue of February 14.

April 1–June 1. Intensive Course in Ophthalmology. Page 240, issue of February 14.

April 4. Hermann M. Biggs Memorial Lecture. Page 206, issue of February 7.

May 13–17. American College of Physicians. Page 798, issue of December 20.

June 20–22. American Association for the Study of Goiter. Notice above.

District Medical Society

WORCESTER

March 13. Worcester Memorial Hospital.
April 10. Hahnemann Hospital.
May 8. Annual meeting.